IBNS
International Behavioral Neuroscience Society

Annual Meeting Program and Abstracts

Hiroshima, Japan
June 26-30, 2017



Abstracts of the 26th Annual Meeting of the International Behavioral Neuroscience Society

Volume 26, June 2017

Contents

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PRESIDENTIAL WELCOME

Mikhail Pletnikov, PhD
IBNS President
Dept. of Psychiatry & Behavioral Science
Johns Hopkins University, School of Medicine
Baltimore, Maryland, USA

Dear Friends and Colleagues,

I am delighted to welcome you to our 26th Annual Meeting of the International Behavioral Neuroscience Society. This is the first meeting to take place in Japan, a country with a vibrant behavioral neuroscience community, the members of which have been involved in founding our society (Professor Yutaka Oomura – 1992-93) and have been Council members during the early years of IBNS (Professors Hitoo Nishino and Toshiie Sakata – 1995-96). When we were discussing places for IBNS 2017, there was a unanimous agreement to go to Asia to expand our presence in this part of the world and to reach out to our long-term colleagues and friends in Japan. In a way, our 2017 meeting is a long-overdue acknowledgement of the contributions the Japanese behavioral neuroscientists have been making to the success of IBNS.

I would like to thank the Chair of the Local Organizing Committee, Professor Yoichi Ueta, and his colleagues for their outstanding help with preparing this meeting in Hiroshima, a city with a rich history and gorgeous nature.

Our special thanks go out to the Program Committee and its Chair, Anthony Kline, and Co-Chair, Elena Choleris. This was another year of hard work and painful decisions to select the best of the best symposium proposals to accommodate them in our standard four-day program. I hope you will enjoy the scientific program that the committee put together for you and will appreciate the effort and dedication of the committee's members. I would also like to thank the Education and Training Committee for choosing the promising early career stage scientists for travel awards. This is a part of the continuous and important mission of the society to foster new generations of behavioral neuroscientists by providing them with the opportunity to attend annual meetings and discuss their research with other delegates.

We are always grateful to our sponsors for their support of our annual meetings. I encourage you to visit their stands and the workshop (organized by Elsevier) during the meeting to find out more about their new products and services.

We greatly appreciate our Executive Director, Marianne Van Wagner and Business & Event Manager, Alison Watson. Their contributions to making our annual meetings enjoyable, hassle-free and financially sustainable are difficult to over-estimate; the current venue is no exception. Please, make sure to stop by the registration desk to personally thank them.

I am looking forward to an outstanding meeting in Hiroshima, Japan.

Best wishes,

Mikhail (Misha) Pletnikov
President IBNS

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AWARDS

Outstanding Achievement Award

The 2017 Outstanding Achievement Award will be presented to Yutaka Oomura, (Professor Emeritus, Kyushu University). IBNS Fellow and member since 1993. He will be awarded a plaque during the IBNS Awards Banquet.

Dr. Yutaka Oomura (born on January 4, 1925 in Kyushu, Japan) is a pioneer in the study of feeding and sexual behaviors, with a focus on the integration of the hypothalamus and the limbic system. Dr. Oomura graduated from Medical School, and was appointed as Professor of Physiology at School of Medicine, Kagoshima University in 1956. His next appointment was as Professor of Physiology at the University of Kanazawa and in 1974 he moved to Kyushu University as Professor of Physiology. He has contributed the IBNS as Fellow and Council member (1993-1995) from Japan. He is the honorary advisor of the Local Organizing Committee for the IBNS 2017 meeting in Hiroshima, Japan.

Early Career Achievement Award

The 2017 Early Career Achievement Award will be presented to Sarah Baracz during the IBNS Awards Banquet. Sarah will receive $500, a waiver for registration fees and will give a talk entitled "*Adolescent oxytocin treatment reverses the effects of early life stress on methamphetamine seeking behavior differently depending on sex*" on Tuesday, June 27, 4:00 p.m.

Sarah completed her PhD 2 years ago, and since then has held a post-doctoral position at the University of Sydney, and most recently at Yale University. Her research during this time has significantly furthered the understanding of the neurocircuitry involved in oxytocin as a therapy for drug addiction, it has progressed the development of novel oxytocin compounds, and has probed the neural mechanisms common to drug addiction and depression. Sarah's clinical skills have enabled her to contribute to public health research in drug addiction in Australia, and she continues to use these skills in ongoing neuropsychological studies in children's hospitals. Sarah has been invited to speak at international meetings, her research is highly cited and has been disseminated through nationally televised media, and she is actively engaged in advocating for women in science. Recently she has received international funding for her own independent project researching the interactions of oxytocin, stress, and addiction. Sarah will soon begin a faculty position at Macquarie University in Sydney, where she will continue her research into the neurobiology of addiction.

TRAVEL AWARDS

We are pleased to announce the recipients of the IBNS Travel Awards for the 2017 meeting in Hiroshima, Japan. Award winners will receive a cash award, certificate, and waiver of registration fees. Travel awardees are presenting orally and will also have their research presented in a poster session. Congratulations to all. Funding for the travel awards has been provided by the generosity of Elsevier Science and the IBNS members.

2017 Travel Award Recipients *(listed alphabetically)*

Samantha Adler, University of Texas Health at San Antonio, San Antonio, TX, United States
Tania Aguilar, Instituto de Neurobiologa, Santiago de Quertaro, Mexico
Angela Caruso, Istituto Superiore di Sanit, Rome, Italy
Marangelie Criado-Marrero, University of South Florida, Tampa, FL, United States
Aarthi Gobinath, University of British Columbia, Vancouver, BC, Canada
Evan Hart, UCLA, Los Angeles, CA, United States
Kelvin Hui, RIKEN Brain Science Institute, Wakoshi, Saitama, Japan
Song-Mao Liao, University of California, San Diego, La Jolla, CA, United States
Melissa Malvaez, UCLA, Los Angeles, CA, United States
Arlene Martinez-Rivera, Weill Cornell Medicine, New York, NY, United States
Richard Matta, University of Guelph, Guelph, ON, Canada
Rachel Navarra, Rowan University School of Medicine, Stratford, NJ, United States
Steven Neal, Randolph-Macon College, Ashland, VA, United States
Christie Pizzimenti, Oregon Health & Science University, Portland, OR, United States
Juan Jair Santillan-Cigales, Universidad Nacional Autonoma de Mexico, Mexico City, Mexico
Abdul-Rahman Suleiman, Wayne State University, Dearborn, MI, United States
Ana Luisa Terzian, FMRP - USP, Ribeirao Preto, Brazil
Mumeko Tsuda, NIMH/NIH, Bethesda, MD, United States
Leigh Walker, Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia
Kira-Elise Wilson, La Trobe University, Melbourne, VIC, Australia
Cameron Woodard, University of British Columbia, Vancouver, BC, Canada
Shunya Yagi, University of British Columbia, Vancouver, BC, Canada
Shenghua Zhu, University of Manitoba, Winnipeg, MB, Canada

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ACKNOWLEDGMENTS

The Society would like to extend our deep appreciation to the following committees that are responsible for the success of this meeting:

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Kiyofumi YAMADA, Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Nagoya

Mikhail Pletnikov (Council Liaison)

Any IBNS member who would like to become more involved in the Society may volunteer to serve on an IBNS committee. Committee details can be found on our website at http://www.ibnsconnect.org/committees

PROGRAM

REGISTRATION: Please pick up your name badge on Monday, June 7, from 2:00-5:00 p.m., before the opening reception in The Grand Prince Hotel. There is no on-site registration – ALL registrations must be made online, prior to the start of the meeting. Name badges are required for ALL events, including the opening reception and closing banquet – no exceptions. There will be a $10 fee for replacement badges. You may also pick up your badge prior to morning sessions each day.

The Grand Prince Hotel is the conference venue and all events will be in the hotel unless otherwise noted.

MONDAY, June 26

8:00-11:00 **Council Meeting.** Council members only. *Sinju Room*

8:00-16:00 **Tours/Free time**. Local touring options with details are listed on the IBNS website. The tour company in the lobby of the Grand Prince Hotel can also advise you.

14:00-17:00 **Registration.** *Main Lobby*

16:30-17:15 **Student/Post-Doc Social.** *Park View Room*
Refreshments and information on IBNS meeting events, competitions and games

17:30-20:00 **Welcome Reception.** *Prince Wedding Suite*

Welcome from University of Hiroshima President, **Mitsuo Ochi**
Welcome from Mayor of Hiroshima, **Kazumi Matsui**
Welcome by Professors **Yutaka Oomura** and **Yoichi Ueta** (Local Organizing Chairs)
Recognition of the IBNS Local Organizing Committee
Welcome from IBNS President, **Mikhail Pletnikov**

Hors d'oeuvres and cash bar

TUESDAY, June 27

Presidential Lecture

08:00-09:00 **Presidential Lecture: Behavioral Neuroscience of Autism**. Toru Takumi. *Setouchi Hall, Room 1-2*

09:05-09:30 **Break – Exhibits.** *Setouchi Hall, Room 3-5*

Symposium: Exercise and brain health across the lifespan. Chairs: Liisa Galea and Cindy Barha. *Setouchi Hall, Room 1-2*

09:30-10:00 **Moderate-intensity aerobic exercise improves cognitive performance and neural efficiency in older adults with vascular cognitive impairment.** Liu-Ambrose, Teresa; Hsu, Chun Liang; Best, John R; Davis, Jennifer C; Nagamatsu, Lindsay S; Wang, Shirley; Boyd, Lara A; Voss, Michelle W; Eng, Janice J; Hsiung, Robin GY.

10:00-10:30 **Sex-specific effect of aerobic exercise on executive function in older adults with vascular cognitive impairment: Importance of BDNF and APOE4.** Barha, Cindy; Hsiung, Robin; Best, John; Jennifer, Davis; Liu-Ambrose, Teresa.

10:30-11:00 **Exercise during pregnancy and the postpartum influences maternal mood and neurogenesis in the dam**. Gobinath, Aarthi R.; Galea Liisa A.M.

Symposium: Dysfunctional neuro-immune system interactions in CNS disorders. Chairs: Jo Neill and Anthony Vernon. *Setouchi Hall, Room 6*

09:30-10:00 **Dysregulated immune mechanisms: impact on psychiatric disorders**. Prinssen, Eric; Malhotra, Dheeraj; Knuesel, Irene; Schobel, Scott.

10:00-10:30 **Abnormal trajectory of rat brain maturation following exposure to maternal immune activation: a longitudinal 1H-MRS and MRI study**. Crum, William, Sawiak, S; So, Po-Wah, Lythgoe, David; Chege, Winfred; Natesan, Sridhar, Cooper, Jonathan; Williams, Steven; Kapur, Shitij; Vernon, Anthony.

10:30-11:00 **Behavioural consequences of maternal immune activation in the offspring**. Neill, Joanna; Fasolino, Victoria; Murray, Katie; Edye, Michelle; Oladipo Joanna; Cadinu, Daniela; Idris, Nagi; Grayson, Ben; Harte, Michael; Knuesel, Irene; Prinssen, Eric.

11:00-11:30 **How do early-life immune dysfunction and stress interact to affect dopamine mediated behaviours in adolescence and adulthood?** Paula M Moran.

11:30-13:30 **Lunch Break**

11:30-12:30 **Scientific Peer Review Process at NIH: tips on submitting and getting a grant.** Markowska, Alicja. *Setouchi Hall, Room 6*

Symposium: Animal model of autism, vulnerable brain area and circuit. Chairs: Jun Nomura and Takeshi Sakurai. *Setouchi Hall, Room 6*

13:30-14:00 **Analysis of mouse models for psychiatric disorders with social behavior alterations**. Sakurai, Takeshi: Nakamura, Yamato.

14:00-14:30 **Disruption of autophagic signaling in murine forebrain affects excitatory-inhibitory balance via mistrafficking of GABAA receptors leading to ASD-like behaviours**. Hui, Kelvin; Takashima, Noriko; Matsukawa, Hiroshi; Watanabe, Akiko; Nilsson, Per; Endo, Ryo; Saido, Takaomi; Itohara, Shigeyoshi; Yoshikawa, Takeo; Tanaka, Motomasa.

14:30-15:00 **CHD8 haploinsufficiency results in autistic-like phenotypes in mice**. Yuta Katayama; Masaaki Nishiyama; Hirotaka Shoji; Yasuyuki Ohkawa; Atsuki Kawamura; Tetsuya Sato; Mikita Suyama; Toru Takumi; Tsuyoshi Miyakawa; Keiichi I. Nakayama.

15:00-15:30 **Phenotypic analysis of a mouse model for 15q25.2-25.3 deletion syndrome**. Nomura, Jun; Kanda, Akifumi; Ellegood, Jacob; Lerch, Jason; Sotomaru, Yusuke; Takumi, Toru.

Symposium: Social stress on drug abuse vulnerability, cognitive function and aggressive behavior. Chairs: Giovanni Biggio and Enrico Sanna. *Setouchi Hall, Room 1-2*

13:30-14:00 **Methamphetamine addiction: activation of multiple stress pathways**. Cadet, Jean Lud.

14:00-14:30 **Early life stress, increased alcohol intake and altered synaptic plasticity**. Giuseppe Talani.

14:30-15:00 **The relationship between stress, drug addiction and aggressive behavior**. Biggio, Giovanni; Sanna, Enrico.

15:00-15:30 **CRF-modulation in VTA-DRN escalates alcohol and cocaine intake after social stress**. Klaus A. Miczek, Lara S. Hwa, Emily Newman, Herbert Covington, Joseph F. DeBold.

15:30-16:00 **Break – Exhibits.** *Setouchi Hall, Room 3-5*

16:00-16:30 **Early Career Achievement Award.** Adolescent oxytocin treatment reverses the effects of early life stress on methamphetamine seeking behavior differently depending on sex. Sarah Baracz. *Setouchi Hall, Room 1-2*

16:30-19:00 **Travel Award Data Blitz.** Chairs: Jill Silverman and Stacey Rizzo. *Setouchi Hall, Room 1-2*

2017 Travel Award Recipients *(listed alphabetically)*

Samantha Adler, University of Texas Health at San Antonio, San Antonio, TX, United States

Tania Aguilar, Instituto de Neurobiologa, Santiago de Quertaro, Mexico

Angela Caruso, Istituto Superiore di Sanit, Rome, Italy

Marangelie Criado-Marrero, University of South Florida, Tampa, FL, United States

Aarthi Gobinath, University of British Columbia, Vancouver, BC, Canada

Evan Hart, UCLA, Los Angeles, CA, United States

Kelvin Hui, RIKEN Brain Science Institute, Wakoshi, Saitama, Japan

Song-Mao Liao, University of California, San Diego, La Jolla, CA, United States

Melissa Malvaez, UCLA, Los Angeles, CA, United States

Arlene Martinez-Rivera, Weill Cornell Medicine, New York, NY, United States

Richard Matta, University of Guelph, Guelph, ON, Canada

Rachel Navarra, Rowan University School of Medicine, Stratford, NJ, United States

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Shenghua Zhu, University of Manitoba, Winnipeg, MB, Canada

WEDNESDAY, June 28

Keynote Speaker

08:00-09:00 **Using the Neurobiology of Will Power to Treat Drug Addiction.** Kalivas, Peter W. *Setouchi Hall, Room 1-2*

09:00-09:30 **Break – Exhibits.** *Setouchi Hall, Room 3-5*

Symposium: Advances in Behavioral Neuroscience in Japan and Diversity of DAergic Regulation. Chairs: Yoichi Ueta and Kiyofumi Yamada. *Setouchi Hall, Room 6*

09:30-09:54 **Memory enhancement by food intake involves epigenetic modulation of BDNF and acidic FGF genes expression.** Yutaka Oomura; Toshihiko Katafuchi.

09:54-10:18 **Behavioral study based on hippocampal theta power**. Sakata, Shogo; Sakimoto, Yuya.

10:18-10:42 **Life-long hormonal and experiential influences on social brain.** Ogawa, Sonoko; Kazuhiro, Sano; Shinji, Tsukahara.

10:42-11:06 **Discovery of a novel reward signal in the striatum**. Taku, Nagai; Keisuke, Kuroda; Kiyofumi, Yamada; Kozo, Kaibuchi.

11:06-11:30 **Coordinated expression of learned motor behavior through striatofugal pathways**. Kobayashi, Kazuto; Iguchi, Yoshio; Nishizawa, Kayo.

Symposium: Neurobiological mechanisms of social and non-social reward. Chairs: Alexa Veenema and Edward Nieh. *Setouchi Hall, Room 1-2*

09:30-10:00 **Lateral Hypothalamic Control of Motivated Behaviors through the Midbrain Dopamine System**. Nieh, Edward H; Vander Weele, Caitlin M; Matthews, Gillian A; Prebrey, Kara N; Wichmann, Romy; Leppla, Christopher A; Izadmehr, Ehsan M; Tye, Kay M.

10:00-10:30 **Nucleus accumbens dopamine D1-receptor-expressing neurons control incentive salience to reward-predictive cues**. Macpherson, Tom, Hikida, Takatoshi.

10:30-11:00 **Neuronal correlates of motivational sensitivity to natural and drug rewards.** O'Donovan, Bernadette; Robke, Rhiannon; Saramanayake, Srimal; Hashemi, Parastoo; Ortinski, Pavel I.

11:00-11:30 **Role of opioid and vasopressin systems in socially rewarding behaviors**. Veenema, Alexa; Smith, Caroline; Bredewold, Remco.

11:30-13:30 **Lunch Break**

11:30-12:30 **Career Development Workshop.** *Setouchi Hall, Room 6*

All levels of trainees are encouraged to attend. In the current funding climate, knowing the value of a PhD career in behavioral neuroscience outside of academia is crucial for professional success. This talk will introduce and expand on various

alternative career options in non-academic environments with a background in neuroscience. A panel of professionals from the fields of industry to government will be present to answer any questions. Please join us!

Symposium: Assessing changes in cognitive and affective behavior in models of acute neurologic injury. Chair: Farida Sohrabji. *Setouchi Hall, Room 6*

13:30-14:00 **Assessing depression in a rodent model of spinal cord injury**. Hook, Michelle; Brakel, Kiralyn; Aceves, Miriam.

14:00-14:30 **Behavioral correlates of TBI neuropathology; underlying mechanisms of escalated alcohol drinking**. Mayeux, Jacques; Stiepler, Zack; Gilpin, Nicholas; Middleton, Jason; Edwards, Scott; Molina, Patricia.

14:30-15:00 **Evaluation of social cognition in neural injury**. Choleris, Elena; Phan, Anna; Matta, Richard; Ervin, Kelsy S.; Kavaliers, Martin.

15:00-15:30 **Targeting effort-related motivational dysfunction in neurological and psychiatric disorders: Animal models**. Salamone, John; Correa, Merce; Yang, Jen-Hau; Rotolo, Renee; Presby, Rose; Yohn, Samantha.

Symposium: Insights from studying contrasting circuits and mechanisms underlying adaptive coping. Chair: Jason Radley. *Setouchi Hall, Room 1-2*

13:30-14:00 **Circuits for the organisation and modulation of defensive behaviour in the rat**. McNally, Gavan. P.

14:00-14:30 **A basal forebrain interface for coordinating endocrine and behavioral responses to stress.** Radley, Jason.

14:30-15:00 **Stress hypothalamic-pituitary-adrenal (HPA) axis habituation is met by differential changes in the serotonergic system of male and female rats.** Viau, Victor.

15:00-15:30 **Prefrontal glucocorticoid signaling mechanisms and stress integration.** Herman, James P.; McKlveen, Jessica M.; Hu, Yueh-Chiang; Mahbod, Parinaz; Morano, Rachel; Scheimann, Jessie; Maoloney, Rachel.

15:30-16:00 **Break – Exhibits.** *Setouchi Hall, Room 3-5*

Symposium: Species-specific signals for protection of the social group. Chairs: Markus Fendt and Yasushi Kiyokawa. *Setouchi Hall, Room 6*

16:00-16:30 **To call or not to call: Assessing the determinants of vocalizing by isolated guinea pig pups**. Hennessy, Michael B.; Schiml, Patricia A.: Deak, Terrence.

16:30-17:00 **Emission of rat vocalizations as the mechanism of ethotransmission**. Brudzynski, Stefan M.

17:00-17:30 **Alarm and appeasing pheromones in rats.** Kiyokawa, Yasushi.

17:30-18:00 **Ultrasonic vocalization in behavioral paradigms of innate and learned fear**. Fendt, Markus; Bergado Acosta, Jorge; Brosch, Marcel; Kahl, Evelyn; Wernecke, Kerstin; Whör, Markus.

Symposium: Drugs of abuse? Beyond the pharmacological reinforcement. Chairs: Christian Müller and Klaus Miczek. *Setouchi Hall, Room 1-2*

16:00-16:30 **Lipid systems mediate the selective antidepressant effects of self-administered alcohol in rodent models**. Christian P. Mueller.

16:30-17:00 **Explaining how the drug, the set and the setting interact to generate different patterns of drug choice in rats**. Serge H. Ahmed.

17:00-17:30 **The reinforcing effects of addictive drugs: it's all about location.** Badiani, Aldo; De Pirro, Silvana.

17:30-18:00 **The CRF system and brief episodes of aggression and defeat: Behavior in Excess**. Klaus A. Miczek, Herbert Covington III, Xiao Han, Michael Leonard and Joseph F. DeBold.

18:00-18:30 **Break – Exhibits.** *Setouchi Hall, Room 3-5*

18:30- 20:30 **Poster Session 1.** *Setouchi Hall, Room 3-5*

1. **Age-related neuroinflammatory responses associated with changes in learning impairments in a mouse model of Alzheimer's disease**. Zhu, Shenghua; Wang, Jun-Feng; Li, Xin-Min.
2. **Up-regulation of astrocyte-derived immune-related genes contributes to behavioral impairment.** Norimichi, Itoh; Taku, Nagai; Akira, Sobue; Daisuke, Ibi; Akira, Nakajima; Toshitaka, Nabeshima; Kiyofumi, Yamada.
3. **Behavioral characterization of Neuropeptide S receptor - deficient mice in animal paradigms of pathological fear.** Kolodziejczyk, Malgorzata; Fendt, Markus.
4. **Neuromodulatory effect of cytokine in the dorsal raphe nucleus and individual difference of aggression**. Aki Takahashi, Hossein Aleyasin, Meghan E. Flanigan, Anna Brancato, Caroline Menard, Madeline L. Pfau, Veronika Kana, Wang Jun, Georgia E. Hodes, Bruce S. McEwen and Scott J. Russo.
5. **Stress-induced alcohol drinking in mice lacking -opioid receptors**. Yuki Moriya; Yoshiyuki Kasahara; F. Scott Hall; George R. Uhl; Kazutaka Ikeda; Ichiro Sora.
6. **Resilience Factors Mediating Social Defeat Stress in Syrian Hamsters**. Markham, Chris; Edwards, Malcolm; Lacey, Tiara, Best, Janae; Smith, Michael.
7. **Impaired visual discrimination learning in Disc1-knockout mice, reversed by clozapine treatment**. Bolati, Wulaer; Taku, Nagai; Akira, Sobue; Keisuke, Kuroda; Kozo, Kaibuchi; Toshitaka Nabeshima; Kiyofumi, Yamada.
8. **The effects of synthetic psychoactive cathinones on lethality and temperature**. Dawn Muskiewicz, F. Scott Hall, Yasir Saber, Federico Resendiz Gutierrez.
9. **Animal models of maternal immune activation and relevance for schizophrenia**. Harms, Lauren; Meehan, Crystal; Dunn, Ariel; Hodgson, Deborah; Michie, Patricia.
10. **The inferior colliculus: An alternative structure for deep brain stimulation in Parkinson's Disease?** Engelhard, Karl-Alexander; Schwarting, Rainer; Melo-Thomas, Liana.

11. **Ultrasounds release catalepsy in rats: A new animal model for paradoxical kinesia**. Tonelli, Luan Castro; Whör, Markus; Schwarting, Rainer; Mel-Thomas. Liana.
12. **Involvement of dopamine and norepinephrine in the sex-specific regulation of social play by vasopressin**. Bredewold, Remco; Nascimento, Nara; Veenema, Alexa.
13. **Blockade of the sigma-1 chaperone impairs brain plasticity induced in mice by habituation to a complex environment, the Hamlet test**. Lucie Crouzier, Olivier Teuf, Anas Rivire, Tangui Maurice.
14. **Transgenic approaches to regulate the neuronal activity in rat vasopressin neuron**. Yoshimura Mitsuhiro, Maruyama Takashi, and Ueta Yoichi.
15. **The effects of blocking nucleus accumbens dopamine D1-type receptors on social learning of food preferences in male and female mice.** Matta, Richard; Russell, Madison J.; Tessier, Danielle J.; Choleris, Elena.
16. **Medial prefrontal cortex versus orbitofrontal cortex: teasing apart differences in plasticity after stress.** Adler, Samantha; Bulin, Sarah; Patton, Michael; Girotti, Milena; Morilak, David.
17. **Effects of preconceptional corticosterone and prenatal antidepressant treatment on stress, responsivity and hippocampal neurogenesis in the next (F2) generation**. Abdul-Rahman Suleiman, Susanne Brummelte.
18. **The effects of clomipramine on anxiety-related behavior and Dnmt3a mRNA expression in the mPFC of male and females rats**. Smith, Dana M.; Higham, Chris; Ransohoff, Jaime; Ragan, Christina M.
19. **Sexual behavior and pair bonding does not increase the number of new cells in the female and male prairie vole (Michrotus ochrogaster).** Aguilar, Tania; Daz, Nstor; Young, Larry; Paredes, Ral; Portillo, Wendy.
20. **Neuroeconomics of Motherhood: Investigating the neurobiological effects of restricted resources and threat presence in lactating maternal rats (Rattus norvegicus).** Scarola, Samantha; Kent, Molly; Bardi, Massimo; Neal, Steven; Perdomo-Trejo, Jose; Thompson, Brooke; Lambert, Skylar; Lambert, Kelly.
21. **Central amygdala relaxin-3/rxfp3 signalling modulates alcohol-seeking in rats**. Walker, Leigh. Kastman, Hanna. Krstew, Elena. Gundlach, Andrew. Lawrence, Andrew.
22. **Time-restricted feeding exerts anti-inflammatory and neuroprotective effects on acute seizure model.** Santillan-Cigales, Juan Jair; Landgrave-Gomez Jorge; Mercado-Gomez Octavio Fabian; Guevara-Guzman, Rosalinda.
23. **Exploring Maternal-Based Neuroplasticity: Neuroanatomical modifications in the rodent prefrontal cortex**. Gibson, Adam; Kinsley, Craig; Kent, Molly; Lambert, Kelly.
24. **A novel automated home-cage task to assess motor skill learning and fine motor control in a mouse model of Huntington's Disease.** Woodard, Cameron L.; Bolanos, Federico; Boyd, James D.; Murphy, Timothy H.; Raymond, Lynn A.
25. **Galanin-3 receptor antagonism by SNAP 37889 blocks cue-induced reinstatement of alcohol seeking in IP rats and increases c-Fos expression in the nucleus accumbens shell**. Wilson, Kira-Elise; Limburg, Sigrid; Duggan, Melissa; Lawther, Adam J.; Williams, Spencer J.; Lawrence, Andrew J.; Hale, Matthew W.; Djouma, Elvan.
26. **Left-right hemispheric functional asymmetry of ventral hippocampus and dorsolateral striatum**. Yukitoshi, Sakaguchi; Yoshio, Sakurai.

27. **Epigenetic involvement of the endocannabinoid vs. endovanilloid system in anxiogenic-like effects of nicotine as a stressor.** Hayase,Tamaki.
28. **Involvement of the rat hippocampal NMDA and AMPA receptors in temporal order memory in radial maze.** Sugita, Manami; Yamada, Kazuo; Ichitani, Yukio.
29. **Multiple functional significance of the glucose-monitoring neuronal network in the medial orbitofrontal cortex**. Szabo, Istvan; Hormay, Edina; Csetenyi, Bettina; Karadi, Zoltan.
30. **Bidirectional modulation of CB1 receptors influences compulsive-like and social interaction behaviors in a non-induced compulsive-like mouse model**. Marth, Tandi E.; Mitra, Swarup; Santana-Miranda, Vanessa; Ghosh Basu, Debarati; Poe, Brooks; Mucha, Mackenzie; Bult-Ito, Abel.
31. **The blockage of ventromedial hypothalamus CRF type 2 receptors impairs escape responses in the elevated T-maze**. Silva, MSCF; Souza, TMO; Pereira, BA; Cespedes. IC;, Bittencourt, JC; Viana, MB.
32. **A non-invasive eye tracking study using rhesus macaques and titi monkeys.** Murai, Takeshi; Freenam, Sara; Palumbo, Michelle; Phi, Casey; Bales, Karen; Bauman, Melissa.
33. **Reduced memory and recognition in prenatal valproic acid-exposed mice model of autism spectrum disorder influence the offspring's function of memory.** Misato, Yoshikawa; Hiroaki, Aso; Masahiko, Watanabe; Katsuya, Suemaru.
34. **Sex differences and modulation by sex hormones of risk-based decision making with acute administration of amphetamine**. Yagi, Shunya; Wainwright, Steven; Lieblich, Stephanie; Floresco, Stan; Galea, Liisa.
35. **Mice that lack zinc transporter 3 (ZnT3) do not exhibit generalized social avoidance following repeated social defeat stress**. McAllister, Brendan; Dyck, Richard.
36. **Timing and amounts of high fat diet intake affect the benefit which improves social avoidance induced by social defeat stress.** Otsuka,Airi; Shiuchi, Tetsuya; Sei, Hiroyoshi.
37. **Cannabinoid type 2 receptors in brain dopamine neurons modulates anxiety-like and psychostimulant behaviors in floxed DAT-Cnr2 mouse model**. Hiroki, Ishiguro; Emmanuel, Onaivi; Ana, Canseco-Alba; Hai-Ying, Zhang; Eliot, Gardner; Zheng-Xiong, Xi; Qing-Rong, Liu.
38. **Effect of oleuropein on cognitive deficits and changes in hippocampal BDNF and cytokine expression in a rat model of post-traumatic stress disorder**. Bombi Lee; Insop Shim;Hyejung Lee; Dae-hyun Hahm.
39. **Effects of Ginsenoside Rb1 on rescues anxiety-like responses in a rat model of post-traumatic stress disorder**. Bombi Lee; Insop Shim, Hyejung Lee; Dae-hyun Hahm.
40. **Gastrodin ameliorates development of depression-related symptoms induced by single prolonged stress in rats**. Bombi Lee; Insop Shi; Hyejung Lee; Daehyun Hahm.
41. **Disconnection between the insular cortex and amygdala accelerates binge-like sugar overconsumption in mice**. Yasoshima, Yasunobu.
42. **A functional polymorphism of the mu-opioid receptor gene is associated with psychological characteristics and left anterior insula volume in the Japanese population.** Kubo, Yumiko; Takeuchi, Hikaru; Kikuchi, Yoshie; Ono, Chiaki; Kasahara, Yoshiyuki; Yu, Zhiqian; Taki, Yasuyuki; Kawashima, Ryuta; Tomita, Hiroaki.
43. **A cohort study on the predictability of the risk of mental health disorders using temporal information of handwriting**. Y. Mashio,T. Yoshizaki, M. Ota, H. Kawaguchi.

44. **Varieties of Attentional Effort: Individual Differences in psychophysiology**. Aminihajibashi, Samira; Hagen, Thomas; Dyhre Foldal, Maja; Halvorsen, Jens; Laeng, Bruno; Espeseth,Espeseth.
45. **Bidirectional modulation of threat processing by reversible pharmacological manipulation of basolateral amygdala in macaques.** Malkova, Ludise; Elorette, Catherine; Castanon, Celestino; Forcelli, Patrick A.
46. **Liposomes treatment antagonized dendritic spine loss and reduction of neurogenesis in hippocampus of chronically stressed rats**. Mostallino, Maria Cristina; Biggio, Francersca; Boi, Laura; Locci, Valentina; Toffano, Gino; Biggio, Giovanni.
47. **Does exercise promote the expression of the resiliency factor Neuropeptide Y in the hippocampus of stressed mice?** Joyner, Tabitha; Alapati, Avani; Gerecke, Kim M.
48. **Habituation of the Startle Response in Zebrafish.** Blaser, R.E., Crawford, M., Muhammed-Menzies, D.
49. **Differential Effects of Visual-Olfactory Maternal Presence Without Physical Contact on Behavior, Endocrine Response and Biogenic Amine Turnover**. Herod, Skyla; Bonnin, Alexandre.
50. **Ephedrine HCL, Curcumin and Turmerone in Neurogenesis and Inhibition of Beta-Amyloid Plaques in Transgenic Mice Models**. Paramasivam,Keerthi.
51. **Subthalamic stimulation ameliorates hyperkinetic movement disorders**. Kuo, C-C ;Tai, C-H.
52. **Effects of caffeine on compulsive-like and anxiety-like behaviors in a non-induced mouse model of Obsessive Compulsive Disorder**. Santana, Vanessa; Marth, Tandi; Poe, Brooks; Hall, Adam; Sweeney, McKenzie; Mitra, Swarup; Bult-Ito, Abel.
53. **Role of enkephalin in dopamine2-receptor expressing neurons in licking microstructure.** Ian A. Mendez; Hoa A. Lam; Stephanie N. Lee; James Boulter; Sean B. Ostlund; Niall P. Murphy; and Nigel T. Maidment.
54. **Disruption of autophagic signaling in murine forebrain affects excitatory-inhibitory balance via mistrafficking of GABAA receptors leading to ASD-like behaviours**. Hui, Kelvin; Takashima, Noriko; Matsukawa, Hiroshi; Watanabe, Akiko; Nilsson, Per; Endo, Ryo; Saido, Takaomi; Itohara, Shigeyoshi; Yoshikawa, Takeo; Tanaka, Motomasa.

THURSDAY, June 29

Keynote Speaker

08:00-09:00 **Dopamine in schizophrenia: from bedside to bench and back**. Abi-Dargham, Anissa. *Setouchi Hall, Room 1-2*

18:00-18:30 **Break – Exhibits.** *Setouchi Hall, Room 3-5*

Symposium: Norepinephrine and executive function: Recent findings. Chairs: Barry Waterhouse and Jill McGaughy. *Setouchi Hall, Room 1-2*

09:30-10:00 **Correlation between psychostimulant-induced alterations of local field potentials within primary visual circuits and improved performance of a sensory signal detection task.** Navarra, Rachel; Clark, Brian; Waterhouse, Barry.

10:00-10:30 **Development of noradrenergic innervation of prefrontal cortex contributes to the ontogeny of executive control during adolescence**. McGaughy, Jill.

10:30-11:00 **Anatomical, elelctrophysiological, and molecular evidence for heterogeneous organization and modular operation of the locus coeruleus-noradrenergic system**. Waterhouse, Barry; Chandler, Daniel.

11:00-11:30 **Modafinil improves cognitive control in humans without inducing hyperactivity**. Zackary A. Cope, Arpi Minassian, Dustin Kreitner, David A. MacQueen, Morgane Milienne-Petiot, Mark A. Geyer, William Perry, and Jared W. Young

Symposium: Neuropeptide modulation of addiction. Chairs: Elvan Djouma and Andrew Lawrence. *Setouchi Hall, Room 6*

09:30-10:00 **Peptide Interactions and Reward-Seeking Behaviour**. Lawrence, Andrew.

10:00-10:30 **Stress and potent-rewards remodel lateral hypothalamic orexin circuits**. Dayas CV, Graham BA, James MH, Campbell EJ, Yeoh JW.

10:30-11:00 **Characterisation of the galanin-3 receptor in drug-seeking behaviour**. Djouma, Elvan.

11:00-11:30 **The role of orexin and dynorphin in modulating mesolimbic dopaminergic projections.** Baimel, Corey; Lau Benjamin, K.; Qiao, Min; Borgland, Stephanie L.

11:30-13:30 **Lunch Break**

11:30-13:30 **Meet the Professionals.** *Seashore Room*

Symposium: Experimental reproducibility: Opportunities over crisis. Chairs: Jill Silverman and Stacey Rizzo. *Setouchi Hall, Room 6*

13:30-14:00 **Lack of generalization of strain and sex across behaviors? Data from the founder strains of the collaborative cross and diversity outbred mouse populations.** Sukoff Rizzo, Stacey J; Onos, Kristen D

14:00-14:30 **Do Rats Rule for Neurodevelopmental Disorders? Evidence from the Shank3 Mutant Rat Model of Phelan-McDermid Syndrome and Autism Spectrum Disorder**. Silverman, Jill L; Berg Elizabeth L; Whör Markus.

14:30-15:00 **Reproducibility of reduced dopamine transporter function recreating bipolar mania-relevant behavior**. Jared W. Young, Zackary A. Cope, Molly Kwiatowski, William Perry, Arpi Minassian, Mark A. Geyer.

Symposium: Molecular basis underlying social competence. Chair: Hideaki Takeuchi. *Setouchi Hall, Room 1-2*

13:30-14:00 **Regulatory mechanisms of social behavior in ants**. Koto, Akiko; Motoyama, Naoto; Tahara, Hiroki; Miura, Masayuki; Keller, Laurent.

14:00-14:30 **The Neurobiology of Social Bonding and Empathy-Related Behaviors in Monogamous Prairie Voles.** Young, Larry J.

14:30-15:00 **Analysis of molecular basis underlying decision making according to social familiarity in small fish, medaka**. Saori, Yokoi; Satoshi, Ansai; Yasuhiro, Kamei; Yoshihito, Taniguchi; Larry, Young; Teruhiro, Okuyama; Takeo, Kubo; Kiyoshi, Naruse; Hideaki, Takeuchi.

15:00-15:30 **Endocrine and mutual gazing regulate human-dog reciprocal communication.** Nagasawa, Miho; Katayama, Maki; En, Shiori; Onaka, Tatsushi, Sakuma, Yasuo; Mogi, Kazutaka, Kikusui, Takefumi.

15:30-16:00 **Break – Exhibits.** *Setouchi Hall, Room 3-5*

Oral Presentations: Session 1 (8 minutes talk; 3 minutes Q&A). Chair: Nii Addy. *Setouchi Hall, Room 1-2*

16:05-16:16 **Evaluating photoperiodic effects on the serotonergic system during a sensitive developmental period**. Siemann, Justin K; Green Noah; McMahon, Douglas G.

16:16-16:27 **Reducing FKBP5 expression in the ventral hippocampus produces a PTSD-like phenotype without affecting anxiety or depressive-like behaviors.** Marangelie Criado-Marrero; Benjamin Lopez-Torres; Cesar Torres Gutierrez; Anixa Hernandez; Maria Colon; Ramon Misla David, Chad A. Dickey; James T. Porter.

16:27-16:38 **Daily oxytocin treatment during abstinence from methamphetamine self-administration in male and female rats: Effects on relapse to drug-seeking, social interaction and anxiety.** Everett, Nicholas; Baracz, Sarah; Cornish, Jennifer.

16:38-16:49 **Nucleus incertus and its neuropeptide relaxin-3 influence perforant path-dentate gyrus synaptic plasticity in rats**. Nategh, Mohsen; Motamedi, Fereshteh.

16:49-17:00 **Reevaluation of rodent compulsive-like, depression-like, and anxiety-like behavioral tests in a non-induced mouse model of OCD**. Abel Bult-Ito.

Oral Presentations: Session 2 (8 minutes talk; 3 minutes Q&A). Chair: Tiffany Donaldson. *Setouchi Hall, Room 6*

16:05-16:16 **Interaction of chronic unpredictable stress and brain trauma on cognitive performance, depressive-like behaviors and immune markers**. Bondi, Corina; Kutash, Lindsay; O'Neil, Darik; Marshall, Ian; Cheng, Jeffrey; de la Tremblaye, Patricia; Kline, Anthony.

16:16-16:27 **Cortical-amygdala circuits for value-based decision making**. Melissa Malvaez, Christine Shieh, Michael Murphy, Venuz Y. Greenfield, Harold G. Monbouquette, and Kate M. Wassum.

16:27-16:38 **TRPV1 receptor modulates different phases of conditioned fear learning**. Terzian, Ana Luisa; Resstel, Leonardo.

16:38-16:49 **Sex differences in behavioral and cellular activational responses to central CRF administration in male and female rats.** Klampfl, Stefanie; Yang, Yi; Chang, Judy; Viau, Victor.

Oral Presentations: Session 3 (8 minutes talk; 3 minutes Q&A). Chair: Farida Sohrabji. *Setouchi Hall, Room 1-2*

17:05-17:16 **A role for the anterior cingulate cortex in the encoding and recall of contextual defensive responses to predatory threats**. De Lima, Miguel A. Xavier; Canteras, Newton Sabino.

17:16-17:27 **D2L receptor-expressing striatal neurons control visual discrimination learning in a touchscreen operant system.** Hikida, Takatoshi; Morita, Makiko; Macpherson, Tom.

17:27-17:38 **BIN1 risk factor-based transgenic mice as a model of specific early phenotypes of presymptomatic Alzheimer disease including recognition memory impairments.** Simonneau Michel; Daudin Rachel; Marechal Damien; Abe Yoshifumi; Loe-Mie Yann; Potier Brigitte; Dutar Patrick; Viard Julia; Lepagnol-Bestel Aude-Marie; Birling Marie-Christine; Pavlovic Guillaume; Herault Yann; Ciobanu Luisa.

17:38-17:49 **Intrauterine undernourishment break down the mirnome that controls proliferation, development and migration of the oligodendrocyte**. Ramírez-Orozco, Paulina; Guadarrama-Olmos, José Carlos; Lara-Lozano, Manuel ; García-Vázquez, Raúl, Jiménez, Ismael and González-Barrios, Juan Antonio.

17:49-18:00 **Individual recognition and face inversion effect in medaka fish (Oryzias latipes)**. Wang, Mu-Yun; Takeuchi, Hideaki.

Oral Presentations: Session 4 (8 minutes talk; 3 minutes Q&A). Chair: Kim Gerecke. *Setouchi Hall, Room 6*

17:05-17:16 **Oxytocinergic projections facilitate male sexual behavior via the spinal gastrin-releasing peptide system.** Takumi, Oti; Keita, Satoh; Keiko, Takanami; Junta, Nagafuchi; John, F. Morris; Tatsuya, Sakamoto; Hirotaka, Sakamoto.

17:16-17:27 **Impact of unhealthy diets on gut microbiome and behavior? studies in rats**. Morris, Margaret J; Beilharz, Jess; Maniam, Jayanthi; Kaakoush, Nadeem.

17:27-17:38 **5-HT1A and 2 adrenergic receptors modulate anxiety-like behavior and impulsivity in selective outbred Long-Evans rats**. Donaldson, S.Tiffany; Niedzielak, Tim; Ravenelle, Becky; Joseph, Marie.

17:38-17:49 **Analysis of topographic memory and hippocampal neurogenesis in mice using the Hamlet Test**. Tangui Maurice, Damien Gilabert, Mireille Rossel, Franoise Trousse, Lucie Crouzier.

17:49-18:00 **Role of brain-derived neurotrophic factor (BDNF) in schizophrenia: studies in BDNF heterozygous and val66met polymorphic mice and rats**. van den Buuse, Maarten; Notaras, Michael; Jaehne, Emily.

18:30-20:30 **Poster Session 2.** *Setouchi Hall, Room 3-5*

1. **Regulation of rapid 17b-estradiol facilitated social recognition by MEK/ERK and PI3K/Akt cell signaling pathways in the dorsal hippocampi of female mice**. Sheppard, Paul; Lumsden, Alanna; Ashley, Jenna; Gumienny-Matsuo, Marika; Choleris, Elena.
2. **Ventral tegmental area L-type calcium channels mediates cue-seeking and dopamine release in the nucleus accumbens core during early withdrawal from cocaine**. Nunes, Eric; Hughley, Shannon, Small, Keri; Rajadhyaksha , Anjali; Addy, Nii.
3. **fMRI study of social exclusion and national identity using a cyberball paradigm**. Hong, Sujin; Moore, Adam; Pernet, Cyril; Morcom, Alexa M.; Roberts, Neil; Krasoulis, Agamemnon; Cram, Laura.
4. **A bottom-up amygdala-cortical circuit controls cue-triggered reward-expectation.** Lichtenberg, Nina; Pennington, Zachary; Greenfield, Venuz; Wassum, Kate.
5. **Retrograde Neurodegeneration of Substantia Nigra Projections to the Striatum following Long term survival after Ischemic Stroke**. Panta, Aditya, Sohrabji, Farida.
6. **The short term effects of acute clomipramine treatment and maternal care on microRNA-16 expression in the dorsal raphe of neonatal rats**. Dufort, Connor; Ragan, Christina M.
7. **Coordination of orofacial motor actions with respiration in the rat during ingestive, exploratory, and foraging behaviors**. Liao, SongMao; Rao, Hiteshwar; Kleinfeld, David.
8. **Lowering luteinizing hormone (LH) prior to hippocampal damage (in an Alzheimer's disease model) can mitigate the loss of spatial memory in female rats.** Thornton, Janice; Chang-Weinberg, Janie; Curley, Emily; Natowicz, Rebecca.
9. **Maternal Brain and Parenting Stress**. Noriuchi, Madoka; Mori, Kumiko; Kamio, Yoko; Kikuchi, Yoshiaki.
10. **Determining the mechanistic relationship between Toxoplasma infection and deficits in amphetamine induced activity**. McFarland, Ross; Weng, Zi Teng; Yolken, Robert H; Pletnikov, Mikhail.
11. **Exosomal MHCI derived from astrocytes leads to behavioral and neuropathological abnormalities in mice**. Akira, Sobue; Norimichi, Ito; Kazuhiro, Hada; Akira, Nakajima; Toshitaka, Nabeshima; Taku, Nagai; Kiyofumi, Yamada.

12. **Olfactory bulbectomy in methamphetamine rat mothers induces impairment in morphological and functional development of their offspring**. Slamberova, Romana; Ruda-Kucerova, Jana; Babinska, Zuzana; Sevcikova, Maria.
13. **Fos expression in the hypothalamus and brainstem after tail suspension in rats.** Takashi Maruyama, Yasuhito Motojima, Mitsuhiro Yoshimura, Hirofumi Hashimoto, Satomi Sonoda, Hiromichi Ueno, Reiko Saito, Yoichi Ueta.
14. **Involvement of iCA1? mPFC pathway in the processing of episodic-like memory in rats**. Li, Jay-Shake; Hung, Hsu-Ching.
15. **Prenatal stress on Gad1-heterozygotes selectively perturbs parvalbumin (PV)-positive GABAergic neurogenesis, GABA synapses and social interaction behavior.** Wang, Tianying; Sinha Adya, Saran; Yanagawa, Yuchio; Kawai, Tomoko; Hata, Kenichiro; and Fukuda, Atsuo.
16. **EEG and heart rate synchronization with oscillating OLED light**. Yuda, Emi; Ogasawara, Hiroki; Yoshida, Yutaka; Hayano, Junichiro.
17. **Rapid estrogenic mediation of oxytocin in social recognition in female mice.** Paletta, Pietro; Ali, Kirstyn; Choleris, Elena.
18. **Abnormalities in perineuronal nets (PNN) and behavior in CSGalNAcT1 knockout mice which lacks a key enzyme in chondroitin sulfate synthesis**. Igarashi, Michihiro; Yoshioka, Nozomu; Takeuchi, Kosei; Tamada, Atsushi; Kitagawa, Hiroshi; Takao, Keizo; Miyakawa, Tsuyoshi.
19. **An open-source 3D video based behavioral analysis systems for rodents and monkeys.** Jumpei Matsumoto; Hiroshi Nishimaru; Yusaku Takamura; Taketoshi Ono; Hisao Nishijo.
20. **Nesfatin-1/NucB2 Neurons in the Hypothalamus and Brainstem Activated by Intraperitoneally Administered Cisplatin in Rats.** Yoichi, Ueta; Mitsuhiro,Yoshimura; Satomi, Sonoda; Hiromichi,Ueno; Yasuhito,Motojima; Reiko,Saito;Takashi,Maruyama; Hiroshi,Hashimoto;Yasuhito,Uezono.
21. **Effects of vestibular lesion on hypothalamic feeding-regulating neuropeptides after being exposed to hyper gravity in mice**. Sonoda, Satomi; Yoshimura,Mitsuhiro; Ueno, Hiromichi; Motojima, Yasuhito; Saito, Reiko ; Maruyama, Takashi; Hashimoto, Hirofumi; Morita, Hironobu; Ueta, Yoichi.
22. **Dorsal raphe serotonin-containing neurons in rats are postsynaptically depolarized by both orexin and ghrelin through PLC-PKC signaling pathway: An in vitro study**. Kim, Juhyon; Ogaya, Masaki; Nakajima, Kazuki;Sasaki, Kazuo.
23. **Behavioral correlates to drug-induced rewiring of striatal circuits**. Adermark, Louise; Licheri, Valentina; Morud, Julia; Lotfi, Amir; Ericson, Mia; Sderpalm, Bo.
24. **Effects of 5-HT1B antagonists on behavior in dopamine transporter knockout mice**. Hall, F. Scott; Saber, Yasir; Elhag, Raghad; Resendiz-Gutierrez, Federico.
25. **Exploring Vocalizations in Adult Interactions: The Risk of Committing a Faux Pas**. Burke, Candace; Kisko, Theresa; Euston, David; Pellis, Sergio.
26. **The Role of the Corpus Callosum on Sustained Attention: A Study of Agenesis of the Corpus Callosum in BTBR T+tf/J Mice**. Hsu, Fang-Wei; Martin, Loren; Iceberg, Erica; Gonzalez, Brandon; Allaf, Gabriel; Ladner, Jonathan; Erskine, Nicole.
27. **Different types of basolateral amygdala neurons show different network-dependent electrophysiological properties**. Yang, Y; Wang, G; Shyue, S.
28. **Mechanisms underlying memory consolidation in sleep**. Pavlides, Constantine; Cho Jiyeon; Krzysztof, Sypniewski.

29. **Androgen receptor overexpression leads to a reversible deficit in fear-conditioning in male mice.** Ramzan, Firyal; Azam, Amber; Swift-Gallant, Ashlyn; Monks, Ashley; Zovkic, Iva.
30. **Sildenafil exerts antianxiety-like effect in male mice via oxytocin.** Hein Min Latt, Hiroaki Matsushita, Yuuri Koga, Hiroyuki Michiue, Teiichi Nishiki and Hideki Matsui.
31. **Ethanol affects acid sphingomyelinase-induced changes in depression/anxiety state of mice**. Kalinichenko, Liubov S.; Reichel, Martin; Kornhuber, Johannes; Mueller, Christian P.
32. **Prevention of behavioral abnormalities in the maternal immune activation model**. Weiner, Ina; Ben-Yehuda Rotem.
33. **Basolateral amygdala and anterior cingulate contributions to effortful choice behavior**. Hart, Evan E; Gerson, Julian; Zoken, Yael; Garcia, Marisella; Izquierdo, Alicia.
34. **An altered neurodevelopmental profile in mice deficient for autism-associated Neurexin1 gene: communicative and motor aspects at an early stage**. Caruso, Angela; Della Notte, Salvatore; Fernandes, Cathy; Scattoni, Maria Luisa.
35. **Ventral tegmental area-Cav1.3 L-type Ca 2+ channels CaMKII/ERK2/CREB signaling is essential for long-term adaptation in AMPARs in the nucleus accumbens**. Martnez-Rivera, Arlene; Giordano, Thomas; Gagan, Kaur; Striessnig Joerg; Addy Nii; Rajadhyaksha, Anjali M.
36. **Adult hippocampal neurogenesis affects behavioral responses to an operant model of frustrative nonreward**. Tsuda, Mumeko C; Karlsson, Rose-Marie; Cameron, Heather A.
37. **Sexual hormones are not sufficient to achieve high sexual receptivity in female mice, sexual experience is required.** P. Marco-Mancls, W. Portillo, RG. Paredes.
38. **New neurons promote behavioral recovery and structural plasticity following a rat model of post-traumatic stress disorder.** Schoenfeld, Timothy J; Rhee, Diane; Martin, Laura; Cameron, Heather A.
39. **Persistent effects of acute stress on fear and drug-seeking in a novel model of the comorbidity between post-traumatic stress disorder and addiction.** Pizzimenti, Christie; Navis, Tommy; Lattal, Matt.
40. **Comparing the antidepressant efficacy of voluntary running and fluoxetine in a rat model of postpartum depression: effects on maternal care, depressive-like behavior, and hippocampal neurogenesis**. Gobinath, Aarthi; Richardson, Robin; Chow, Carmen; Workman, Joanna; Lieblich, Stephanie; Barr, Alasdair; Galea Liisa.
41. **Embracing nature's social network: The effect of an engaging environment on social responsiveness and oxytocin-immunoreactivity.** Neal, Steven; Kent, Molly; Bardi, Massimo; Scarola, Samantha; Perdomo, Jose; Thompson, Brooke; Lambert, Skylar; Lambert, Kelly.
42. **Elucidating the neural circuitry of Social Familiarity induced Anxiolysis (SoFiA)**. Majumdar,Sreeparna; Lungwitz,Elizabeth; Bharadwaj,Nikhil; Andrews,Katharine; Dietrich,Amy; Truitt,William.
43. **The effects of JC3 on carrageenan/kaolin induced knee arthritis in rats**. Bongjun, Sur; Seikwan, Oh.
44. **The role of astrocyte DISC1 in cognitive behaviors**. Terrillion, Chantelle E., Crawford, Joshua A., Shevelkin, Alex, Kim, Sung Hong, Fukudome, Daisuke, Sawa, Akira, Kamiya, Atsushi, and Pletnikov, Misha V.
45. **Orexin modulates synaptic transmission in the central vestibular system.** Jiang, Yuan; Lam, Tsz Fung; Ma, Chun Wai; Shum, Daisy Kwok Yan; Wang, Jian Jun; Chan, Ying Shing.

46. **Early life stress can elicit some Schizophrenia-like symptoms in the dopamine transporter heterozygous mice**. David Groenewoud, Leanne Mak Hui Min, Toh Jia Min, Peiyan Wong.
47. **Representation of delay discounting in hippocampus and medial prefrontal cortex**. Masuda, Akira; Sano, Chie; Fujisawa, Shigeyoshi; Itohara, Shigeyoshi.
48. **Prebiotic-mediated changes in attention in healthy human population**. Attila Toth, Zhinoo Amiri, Zoltan Vizvari, Kitti Mintal, Laszlo Lenard, Zoltan Karadi, Renata Cserjesi.
49. **Testing the influence of different conditions on passive and active fear responses in a shock-based avoidance paradigm: behavioral and circuit analysis**. Viellard, Juliette; Herry, Cyril; Canteras Neuwton Sabino.
50. **The quality of the living environment affects the fluoxetine treatment outcome**. S. Poggini, A.Viglione, G. Matte Bon, S. Alboni, S. Garofalo, L. Maggi, I. Branchi.
51. **Seizuring and cognitive long-term effects of a bad first-line antiepileptic treatment choice on the following-line treatment efficacy in a mouse model of absence epilepsy**. Hadjadj, Sarah; Kuchenbuch, Mathieu; Dieuset, Gabriel; Costet, Nathalie; Biraben, Arnaud; Martin, Benot.
52. **Bi-directional modulation of impulsive behavior by the subthalamic nucleus.** Piszczek, Lukasz; Constantinescu, Andreea; Pekcec, Anton; Nicholson, Janet; Haubensak, Wulf.
53. **Genetic background is a significant driver of Alzheimer's disease associated phenotypes**. Onos, Kristen; Keezer, Kelly; Acklin, Casey; Jackson, Harriet; Cossette, Travis; O'Rourke, Rita; Sukoff Rizzo, Stacey J.; Howell, Gareth.

FRIDAY, June 30

Keynote Speaker

08:00-09:00 **The female rat preoptic area contains discrete sets of efferent estrogen-sensitive neurons for proceptive or receptive component of sexual behavior.** Yasuo, Sakuma. *Setouchi Hall, Room 1-2*

09:00-09:30 **Break – Exhibits.** *Setouchi Hall, Room 3-5*

Symposium: Overlapping neural mechanisms mediating substance abuse and depression. Chair: Nii Addy. *Setouchi Hall, Room 1-2*

09:30-10:00 **Overlapping ventral tegmental area cholinergic mechanisms mediating cue-induced drug-seeking and behavioral responses to stress and anxiety.** Nii A. Addy, Eric J. Nunes, Keri M. Small, Shannon Hughley, Lillian Bitner, and Sofia Walton.

10:00-10:30 **Cacna1c (Cav1.2) as a candidate risk gene for the effects of stress on mood-related and cocaine-seeking behavior**. Rajadhyaksha, Anjali; Bavley, Charlotte, Burgdorf, Caitlin.

10:30-11:00 **Orexin's are mediators of vulnerability to the effects of stress**. Laura Grafe and Seema Bhatnagar.

11:00-11:30 **The CRF and Dynorphin systems in the central amygdala differentially control escalation of nicotine intake and negative emotional states.** George, Olivier.

Symposium: Pharmacological and environmental strategies to enhance cognition. Chairs: Riccardo Brambilla and Lorenzo More. *Setouchi Hall, Room 6*

09:30-10:00 **The role of Mitogen and Stress activated protein Kinase 1 in response to environmental enrichment, a possible target for nootropics?** More, Lorenzo; Privitera, Lucia; Frenguelli Bruno.

10:00-10:30 **Strategies for countering spine defects and promoting learning in aging and developmental intellectual disability disorders: Ampakines and environmental enrichment**. Lauterborn, Julie; Lynch, Gary; Gall, Christine.

10:30-11:00 **Dysbindin-1 genetics modulate cognitive responses to antipsychotics through D2-related mechanisms within the prefrontal cortex**. Scheggia, Diego; Mastrogiacomo, Rosa; Mereu, Maddalena; Sannino, Sara; Straub, Richard E.; Armando, Marco; Manag, Francesca; Piras, Fabrizio; De Luca, Maria A.; Weiberger, Daniel R.; Spalletta, Gianfranco; Papaleo, Francesco.

11:00-11:30 **Ras-ERK signalling in Intellectual Disability and Autism Spectrum Disorder: a pathway to the cure?** Brambilla, Riccardo.

11:30-13:30 **Lunch Break**

11:30-12:30 **Workshop:** Elsevier Publishing Connect Workshop. *Setouchi Hall, Room 6*

After attending this free workshop, one in the Elsevier Publishing Connect Workshop series, participants will have an idea of the steps required to be taken before starting to write a paper. They will also be able to plan writing manuscripts using the logical step sequence – not the sequence in which the paper will be read. Authors are also made aware of what aspects of their papers Editors, Reviewers, and Publishers look at critically, and can ensure that in taking care of these areas, their papers are more likely to be accepted. Sensitive areas such as publishing ethics, plagiarism, duplicate publishing, etc. are also explained such that participants have a clear understanding of what their responsibilities are, what is allowed, and what is not permitted.

Symposium: Estrogenic regulation of social behavior. Chair: Sonoko Ogawa. *Setouchi Hall, Room 1-2*

13:30-14:00 **Estrogen action on neural network of social behavior in mice**. Ogawa, Sonoko.

14:00-14:30 **Sexual differentiation of novel sexually dimorphic nucleus of dorsal hypothalamus in mice.** Tsukahara, Shinji.

14:30-15:00 **Rapid actions of estrogens on social behaviour**. Vasudevan, Nandini; Clark, Sara; Rainville, Jennifer; Anchan, Divya.

15:00-15:30 **Estrogenic regulation of social recognition and social learning in mice**. Choleris, Elena; Phan, Anna; Lymer, Jennifer M.; Sheppard, Paul A. S.; Clipperton-Allen, Amy E.; Ervin, Kelsy S.; Gabor, Christopher S.; Paletta, Pietro.

Symposium: Modeling dimensions of neuropsychiatric disorders. Chairs: Noboru Hiroi and Francis Lee. *Setouchi Hall, Room 6*

13:30-14:00 **Deconstructing 22q11.2 copy number variants into dimensions of schizophrenia and autism**. Noboru Hiroi, PhD.

14:00-14:30 **Impact of common polymorphisms on the developmental regulation of fear learning and anxiety behavior**. Lee, Francis.

14:30-15:00 **Endophenotype in the brain: A key concept for understanding the relationships between genes and behavior**. Tsuyoshi Miyakawa.

15:00-15:30 **Unraveling the dimension of 16p11.2 copy number variant syndromes, a comparative studies using rodent models**. Herault, Yann; Nalesso, Valrie; Martin Lorenzo, Sandra; Arbogast,Thomas.

15:30-16:00 **Break – Exhibits.** *Setouchi Hall, Room 3-5*

Symposium: Synthetic psychoactive cathinones (i.e., "bath salts"): Separating fact from fiction. Chair: Frank Hall. *Setouchi Hall, Room 6*

16:00-16:30 **Assessment of the Aversive and Rewarding Effects of Synthetic Cathinones: Implications for Drug Use and Abuse**. Riley, Anthony L.; Nelson, Katherine; Woloshchuk, Claudia J.

16:30-17:00 **Preclinical evaluation of the addictive potential of new synthetic cathinones**. Xu, Peng; Wang, Dan; Wang, Youmei; Shen, Hao-wei.

17:00-17:30 **Synthetic psychoactive cathinones and neurotoxic amphetamines: Critical structural elements that determine neurotoxicity**. Kuhn, Donald M.; Angoa-Perez, Mariana; Anneken, John H.

17:30-18:00 **Lethal and toxic effects of synthetic psychoactive cathinones**. Hall, F. Scott; Muskiewicz, Dawn; Saber, Yasir; Resendiz-Gutierrez, Federico.

Symposium: Insulin and glucose: What's new in metabolic regulation of memory? Chair: Ewan McNay. *Setouchi Hall, Room 1-2*

16:00-16:30 **Insulin, glucose, and beta-amyloid: a tale of three molecules.** McNay, Ewan C.; Pearson-Leary, Jiah; Osborne, Danielle M.

16:30-17:00 **Impaired memory and hippocampal function on a high-fat diet: Sex-differences in hormonal regulation, metabolism, neuronal excitability, and insulin-sensitivity**. Thompson, Lucien T.; Tandon, Neha R.; Underwood, Erica L.

17:00-17:30 **Maintaining insulin signaling to offset cognitive decline with aging**. Thibault, Olivier.

17:30-18:00 **Glucocorticoid regulation of tau pathology in obesity and diabetes**. Dey Aditi; Hao Shuai; Wosiski-Kuhn Marlena; Stranahan Alexis M.

18:00-19:00 **IBNS Business Meeting** – Open to ALL members. *Setouchi Hall, Room 1-2*

20:00-24:00 **IBNS Awards Banquet and Entertainment.** *Setouchi Hall, Room 3-5*

ABSTRACTS

TUESDAY, June 27

08:00-09:00 **Presidential Lecture: Behavioral Neuroscience of Autism**. Toru Takumi. *Setouchi Hall, Room 1-2*

Behavioral Neuroscience of Autism. Toru Takumi, MD, PhD. RIKEN Brain Science Institute. Autism spectrum disorder (ASD) is a complex psychiatric illness that has received considerable attention as a developmental brain disorder. Substantial evidence suggests that chromosomal abnormalities including copy number variations (CNV) contribute to autism risk. The duplication of human chromosome 15q11-13 is known to be the most frequent cytogenetic abnormality in ASD. We have modeled this genetic change in mice using chromosome engineering to generate a 6.3-Mb duplication of the conserved linkage group on mouse chromosome 7. Mice with a paternal duplication (*patDp/+*) display autistic-like behavioral features such as poor social interaction and behavioral inflexibility, and exhibit abnormal ultrasonic vocalizations. This chromosome-engineered mouse model for ASD (*15q dup* mouse) seems to replicate various aspects of human autistic phenotypes and validates the relevance of the human CNV. This *15q dup* mouse is the first CNV model of ASD and a founder mouse for forward genetics of a developmental brain disorder. Our multi-dimensional approach reveals that *15q dup* mice show impaired spine phenotypes, abnormality in serotonin, and excitatory/inhibitory imbalance. The rescue experiment during the developmental stage suggests the significance of serotonin on neural and behavioral development. I'll talk about our recent analyses mainly on the *15 dup* mice and hopefully add our new direction towards understanding the pathophysiology of ASD and development of its therapeutic intervention. Behavioral neuroscience combined with genetics and other cutting-edge technologies will provide new pathophysiological bases for ASD.

09:30-11:00 **Symposium: Exercise and brain health across the lifespan.** Chairs: Liisa Galea and Cindy Barha. *Setouchi Hall, Room 1-2*

Moderate-intensity aerobic exercise improves cognitive performance and neural efficiency in older adults with vascular cognitive impairment. Liu-Ambrose, Teresaa, Hsu, Chun Lianga, Best, John Ra, Davis, Jennifer Ca, Nagamatsu, Lindsay Sb, Wang, Shirleya, Boyd, Lara Aa; Hsiung, Voss, Michelle Wc, Eng, Janice Ja. Robin GYa. aUniversity of British Columbia, Vancouver, British Columbia, Canada, bWestern University, London, Ontario, Canada, cUniversity of Iowa, Iowa City, Iowa, USA. Worldwide, vascular cognitive impairment (VCI) is the second most common type of cognitive dysfunction and is due to cerebrovascular disease. While targeted aerobic training (AT) is a promising approach to delay the progression of VCI by reducing cardiometabolic risk factors, few randomized controlled trials to date have specifically assessed the efficacy of AT on cognitive and brain outcomes in this group at-risk for functional decline. Thus, we conducted a six-month randomized controlled trial to examine the effect of moderate-intensity AT on executive functions and functional neural activity among older adults with mild subcortical ischaemic VCI (SIVCI). Seventy older adults with mild SIVCI were randomly assigned to: 1) 6-month, 3x/week AT or 2) usual care (CON). A subset of participants completed functional magnetic resonance imaging (fMRI) sessions at baseline and trial-completion. During the fMRI sessions, behavioural performance on the Eriksen flanker task and task-evoked neural activity were assessed. At trial completion, after adjusting for baseline general cognition, total white matter lesion volume, and flanker performance, compared with

the CON group, the AT group significantly improved flanker task reaction time. Moreover, compared with the CON, the AT group demonstrated reduced activation in the left lateral occipital cortex and right superior temporal gyrus. Reduced activity in these brain regions was significantly associated with improved (i.e., faster) flanker task performance at trial completion. AT among older adults with mild SIVCI can improve executive functions and neural efficiency of associated brain areas. Future studies with greater sample size should be completed to replicate and extend these findings. Funding: This work was supported by Canadian Stroke Network and the Heart and Stroke Foundation of Canada to TLA and the Jack Brown and Family Alzheimer Research Foundation Society to TLA.

Sex-specific effect of aerobic exercise on executive function in older adults with vascular cognitive impairment: Importance of BDNF and APOE4. Barha, Cindy1,3; Hsiung, Robin2,3; Best, John1,3,4; Jennifer, Davis1,3,4; Liu-Ambrose, Teresa1,3,4. 1Aging, Mobility, and Cognitive Neuroscience Lab, Department of Physical Therapy, University of British Columbia, Vancouver, Canada; 2Division of Neurology, University of British Columbia, Vancouver, Canada; 3Djavad Mowafaghian Centre for Brain Health, Vancouver, Canada; 4Centre for Hip Health and Mobility, Vancouver, Canada.Aerobic training (AT) is a promising, non-pharmacological strategy to mitigate the deleterious effects of aging on brain health. However, a large amount of variation exists in its efficacy. Biological sex may be an important moderator of the relationship between exercise and cognition. Few studies have directly examined this possible sex difference. Evidence also suggests that brain derived neurotrophic factor (BDNF) may mediate the effect of AT on cognition. Thus, we examined whether the beneficial effect of AT on cognitive function as well as BDNF is dependent on sex in older adults with subcortical ischemic vascular cognitive impairment (SIVCI). We conducted a secondary analysis of data acquired from a proof-of-concept randomized controlled trial of a 6-month AT intervention (3x/week). Executive functions was assessed at baseline, trial completion (6 months after randomization), and 6-month post-completion (i.e., follow-up) using: 1) Trail Making Test (TMT; set-shifting); 2) Verbal digits forward and backward (DFB; working memory); 3) Stroop Test (response inhibition). BDNF levels were measured at baseline and trial completion. Analysis of covariance was conducted separately for each executive test and BDNF levels, with sex and intervention (AT vs. usual care control) as fixed effects and controlling for baseline score, global cognitive function (MoCA), and age. At trial completion, AT enhanced performance on the TMT compared to control, but only among females ($p < 0.013$) and not in males ($p > 0.122$). At follow-up, the beneficial effect of AT in females was retained compared to males ($p < 0.003$). Performance on the DFB and Stroop was not significantly influenced by AT or sex (all p's > 0.05). Within the AT group, BDNF levels increased in females (1.569□1.01 ng/ml) but decreased in males (-2.547□1.01 ng/ml) ($p < 0.012$) from baseline to trial completion. In an exploratory analysis, we found that the sex difference in AT efficacy favoring females was evident mainly in carriers of the APOE ε4 allele. Our results suggest that biological sex along with APOE4 genotype can moderate AT efficacy on cognitive health in older adults with SIVCI and that BDNF may be involved. This knowledge highlights the importance of identifying and understanding key moderators of exercise efficacy to allow for evidence-based, sex-specific exercise recommendations that go beyond the 'one-size-fits-all' approach to successfully combat dementia.

Exercise during pregnancy and the postpartum influences maternal mood and neurogenesis in the dam. Aarthi R. Gobinath[1,3] Liisa A.M. Galea Ph.D.[1, 2, 3], [1]Djavad Mowafaghian Centre for Brain Health, University of British Columbia, 2215 Wesbrook Mall, Vancouver, BC, CANADA, V6T1Z3; [2]Department of Psychology, University of British Columbia, [3]Program in Neuroscience, University of British Columbia. Pregnancy and postpartum are associated with fluctuations in steroid hormones and an increased risk to develop

neuropsychiatric disorders. Postpartum depression (PPD) affects approximately 15% of mothers and can adversely affect her offspring. The first-line of pharmacological defense for PPD are SSRIs such as fluoxetine. However, fluoxetine can remain active in breastmilk and directly influence child development. Thus, mothers are hesitant to use SSRIs. However, non-pharmacological therapies such as exercise may be better tolerated and show better efficacious in the postpartum compared to pharmacological manipulations. To investigate this, we treated rat dams daily with high levels of corticosterone (40 mg/kg), to induce a depressive-like phenotype, or oil during the postpartum period. Within the oil and corticosterone conditions, four additional antidepressant groups were created: 1. Fluoxetine (Prozac; 10 mg/kg) + exercise (voluntary access to running wheel); 2. Fluoxetine + no exercise; 3. Saline (vehicle for fluoxetine) + exercise; 4. Saline + No exercise. Dams were tested for alterations in maternal behavior and depressive-like behavior (forced swim test). We also quantified serum corticosterone levels as well as doublecortin (marker of immature neurons) expression in dorsal and ventral dentate gyrus. Daily running activity was recorded and using a median split, dams were further categorized as "high-running" or "low-running." Preliminary results reveal that maternal fluoxetine prevented corticosterone-induced disruptions in maternal care in no running and high running dams whereas low running alone prevented corticosterone-induced disruptions in maternal care. Exercise decreased depressive-like behavior (immobility in the forced swim test) while corticosterone increased depressive-like behavior. Finally, high-running dams exhibited increased expression of doublecortin (immature neurons) in ventral, but not dorsal, dentate gyrus in comparison to no-running dams. Fluoxetine increased doublecortin expression under exercise conditions but not under sedentary conditions. Our findings show that maternal pharmacological and non-pharmacological treatments can interact to differentially affect the well-being of the mother at the behavioral, endocrine, and hippocampal levels.

09:30-11:00 **Symposium: Dysfunctional neuro-immune system interactions in CNS disorders.** Chairs: Jo Neill and Anthony Vernon. *Setouchi Hall, Room 6*

Dysregulated immune mechanisms: impact on psychiatric disorders. Eric P Prinssen, Dheeraj Malhotra, Irene Knuesel, Scott Schobel. Roche Innovation Center Basel, Pharma Research and Early Development, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, Basel, CH 4070, Switzerland eric.prinssen@roche.com. Epidemiological studies have shown a clear association between maternal infection and schizophrenia in the progeny. This maternal immune activation (mIA) is thought to lead to immune priming in the offspring and – together with genetic and other environmental risk factors - to result in a deviation from a normal development trajectory leading to schizophrenia or other CNS disorders. Data is accumulating that immune abnormalities are present throughout the trajectory of subjects that eventually develop schizophrenia as well as during the different phases of disease. Reported abnormalities include microglia number and function, astrocyte and oligodendrocyte functions, blood cytokine and C-Reactive Protein levels, serum NMDA-R autoantibody levels or pathogenicity, and brain complement component 4 expression (explaining part of schizophrenia's strongest genetic association at a population level, i.e. variation in the MHC locus). We will review this clinical evidence in light of potential symptomatic, disease-modifying and preventive treatment strategies, and discuss how mIA animal models may contribute to the implementation of these strategies.

Abnormal trajectory of rat brain maturation following exposure to maternal immune activation: a longitudinal 1H-MRS and MRI study. William R. Crum1; Stephen J. Sawiak2; Po-Wah So1, David J. Lythgoe1, Winfred Chege3, Sridhar Natesan3, Steven C.R. Williams1, and Shitij Kapur3 Anthony C. Vernon3, 4, 5. 1Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's

College London. 2Wolfson Brain Imaging Centre, University of Cambridge. 3Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London. 4Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London. 5MRC Centre for Neurodevelopmental Disorders, King's College London. E-mail: anthony.vernon@kcl.ac.uk. Environmental or genetic disturbances of brain maturation may underlie the pathophysiology of adult-onset psychiatric disorders. We therefore followed the trajectories of brain structural and prefrontal cortex metabolite abnormalities from adolescence to adulthood in rats born to mothers exposed to the viral mimic polyriboinosinic-polyribocytidylic acid (poly-I:C) in pregnancy. Sprague-Dawley rat dams were exposed to poly-I:C (4 mg/kg, i.v. n=5) or 0.9% saline, (i.v; n=5) on gestational day (GD) 15. Male offspring from poly-I:C (n=10 from 5 litters) and saline exposed (n=10 from 5 litters) underwent longitudinal in vivo sMRI and 1H-MRS with a voxel placed in the prefrontal cortex, at post-natal day (PND) 50, 100 and 180. Longitudinal sMRI data were analysed using semi-automated segmentation and tensor based morphometry (TBM). Longitudinal 1H-MRS data were analysed using LC model. Both MRI and MRS data were analysed using linear mixed effect models with age, mIA and treatment as factors, respectively, using SPSS (v22, IBM) with alpha=0.05. Exposure to mIA resulted in subtle age-dependent metabolic perturbations of the normal maturing prefrontal cortex, including decreased glutathione ($p<0.05$; $d=1.08$), taurine ($p<0.01$; $d=1.35$) and N-acetyl-aspartate ($p<0.05$; $d=1.05$) at PND180. Longitudinal sMRI analyses revealed that exposure to mIA decreased hippocampus volume at PND90 and 180 ($p<0.05$; $d=1.07$). TBM revealed widespread grey and white matter alterations across brain maturation (q=0.1 FDR corrected). Prenatal exposure to mIA interferes with postnatal brain maturation, further work is now required to link this to behavioural dysfunction and establish the cellular correlates of the imaging phenotype.

Behavioural consequences of maternal immune activation in the offspring. Joanna C Neill1, Victoria Fasolino1, Katie Murray2, Michelle E Edye4, Joanna Oladipo1, Daniela Cadinu1, Nagi Idris1, Ben Grayson1, Michael K Harte1, Irene Knuesel3, Eric Prinssen3. 1. Division of Pharmacy & Optometry, University of Manchester, M13 9PT, UK. 2. Dept. of Neurology and Neuroscience, Yale University, New Haven, Connecticut, 06510. 3. Roche Innovation Center Basel, 124 Grenzacherstrasse, Basel, CH 4070, Switzerland. 4. Kings College London. Maternal immune activation (mIA) by administration of the viral-mimetic polyriboinosinic-polyribocytidylic acid (poly-I:C) is a key model for neurodevelopmental disorders (NDDs) such as schizophrenia (see Knuesel et al. 2014 for review). Our overall aim is to establish this model in rats. Our initial aim was to establish a strain, dose and dosing regimen of poly I:C to induce a robust systemic inflammatory response in rats. Once established, we have investigated the behavioural consequences of mIA in male and female offspring at specific developmental time points. Female Wistar, Lister Hooded and Sprague Dawley rats (n=8; 10-weeks old) were injected intraperitoneally (i.p) with poly I:C (5-15mg/kg) or saline. Subsequently, female Wistar rats (n=8) were treated with poly I:C (2.5-10mg/kg, i.p.) or saline over 5 consecutive days. Changes in core body temperature and weight were measured prior to treatment, 3h and 6h post-poly I:C. Changes in IL-6, TNFα, IL-1β expression were measured in plasma by ELISA 3h after poly I:C. Behavioural consequences of poly I:C treatment at GD15 in pregnant Wistar dams were assessed using open field and elevated plus maze for anxiety-like behaviour, novel object recognition (NOR) and location for short term recognition memory and social interaction. These tests were conducted at adolescence, postnatal day (PND) 35-45 and again at young adulthood PND 65-68 (social interaction, NOR and Y maze test for working memory). At PND 80 onwards rats were tested for executive function using the attentional set shifting task and once again in NOR. 10 mg/kg Poly I:C produced a significant but variable increase in IL-6 and increase in body temperature in all rat strains 3h

post- injection. TNFα was significantly increased in Wistar (P<0.05) and Sprague Dawley rats (P<0.05) only. 5 Day administration of poly I:C (10mg/kg, i.p.) a significantly increased IL-6 and TNFα (P<0.001) in Wistars on day 1 only. Poly I:C induced a significant increase in IL6 and reduction in body temperature in pregnant Wistar dams (n=5 vehicle, 6 poly I:C) 3 h post dosing (P<0.01). Small sex specific effects on behaviour were observed at adolescence and young adulthood. A significant and robust impairment in attentional set shifting was observed in female poly I:C offspring compared with vehicle on PND 80-90. Poly I:C rats had a significant increase in trials to criterion compared with vehicle rats (P<0.001). In the same rats, a significant NOR deficit was also observed at this time point. We have established a robust model of mIA in Wistar rats and used this to identify the longitudinal development of behavioural changes. Poly I:C induced the most robust IL6 response in Wistar rats, at a dose of 10 mg/kg i.p. mIA resulted in modest behavioural changes at adolescence and young adulthood, and more robust cognitive deficits at PND 90. The neurobiological mechanisms for these behavioural effects are currently being investigated. Sources of financial sponsorship: This work is supported by Roche, the University of Manchester MRC Confidence in Concept scheme, and an MRC DTP studentship awarded to Victoria Fasolino.

How do early-life immune dysfunction and stress interact to affect dopamine mediated behaviours in adolescence and adulthood? PM Moran. University of Nottingham, UK. There is accumulating evidence that dysfunction of the immune system plays a role in dopamine related CNS disorders such as schizophrenia. There is also evidence that dopamine plays a role in the regulation of inflammatory responses involved in autoimmune disorders such as lupus. Early-life immune system dysfunction can have significant behavioural consequences in adulthood, while conversely early-life behavioural stressors can manifest as dysregulated immunity in adulthood. This presentation will review the comparative behavioural evidence for effects of early-life immune dysfunction and early life stressors. Evidence will be considered in the context of the neuroimmune network hypothesis (Nusslock & Miller, 2016, Biological Psychiatry, 80: 23-32) and will evaluate whether dopamine mediated behaviours might be especially vulnerable to early life neuro-immune dysfunction.

11:30-12:30 **Scientific Peer Review Process at NIH: tips on submitting and getting a grant.** Markowska, Alicja. *Setouchi Hall, Room 6*

Scientific Peer Review Process at NIH: tips on submitting and getting a grant. Alicja L. Markowska PhD, DSc, National Institute of Health, National Institute on Aging, Scientific Review Branch, Bethesda, USA. This presentation will provide an overview of the NIH grant mechanisms, the importance of choosing the appropriate Institute and funding opportunity, and highlight common issues in preparing a grant application. Phases of scientific peer review will be explained to answer common questions such as: where does your application go, how does the review get organized, and how does the review proceed. Briefly, after your grant application is sent to NIH, it undergoes a two-tiered review process: initial peer review and Institute/Center Advisory Council review. A Scientific Review Officer (SRO), who identifies reviewers that can best review the application, will conduct the initial review and will be responsible for ensuring that each application receives an objective and fair evaluation. The priority score and Summary Statement will be made available to the applicant through the NIH Commons. The scoring system, review criteria, importance of adequate roster, and other strategies for success will be further discussed at the session.

13:30-15:30 **Symposium: Animal model of autism, vulnerable brain area and circuit.** Chairs: Jun Nomura and Takeshi Sakurai. *Setouchi Hall, Room 6*

Analysis of mouse models for psychiatric disorders with social behavior alterations. Takeshi Sakurai, Yamato Nakamura. Medical Innovation Center, Kyoto University Graduate School of Medicine. Social behavior is important for our everyday life and affected in many psychiatric disorders such as autism, schizophrenia, and mood disorders. Prefrontal cortex (PFC) plays important roles especially in social behaviors acquired after birth, which involves acquisition of cognitive functions, e.g., decision making and working memory. Establishment of PFC local circuitry as well as its connections with other brain areas begins during postnatal development and continues till young adult. Although myelination and inhibitory neuron maturation, both critical for local circuitry formation, seem to take place around 3-4 weeks after birth, other aspects of maturation processes take place during adolescence, and we have been trying to clarify the late events of PFC development during adolescence including neuromodulation system. Williams Beuren syndrome (WBS) is a neurodevelopmental disorder caused by deletion of one copy of chromosome 7q11.23 region, exhibiting characteristic behavioral and cognitive phenotypes, one of which is hypersocial behavior. Gtf2i is one of genes in the chromosome region and heterozygous mice of Gtf2i showed exaggerated social interest in a social habituation paradigm, mirroring hypersociability in WBS patients. Social habituation paradigm requires perception and adjustment of value of repeated social stimuli, involving PFC functions. In order to clarify brain circuitry for social habituation, activity mapping has been performed using both wild type and Gtf2i heterozygous animals. During the process, activation of PFC as well as other brain regions important for social behavior was observed, accompanied by suppression of some of the activation in several social brain areas after repeated social stimuli. This activation profile may be regulated by neuromodulation. By identifying circuitry involving PFC important for social behavior together with its developmental processes, and correlating the circuitry with behavioral outcomes, we hope to clarify mechanisms of social behavior alterations observed in WBS and autism that may involve PFC dysfunction caused by alterations of developmental processes in PFC. Supported by Kakenhi from Ministry of Education, Culture, Sports, Science and Technology in Japan.

Disruption of autophagic signaling in murine forebrain affects excitatory-inhibitory balance via mistrafficking of GABAA receptors leading to ASD-like behaviours. Kelvin Hui1, Noriko Takashima1, Hiroshi Matsukawa1,3, Akiko Watanabe2, Per Nilsson4, Ryo Endo1, Takaomi Saido4, Shigeyoshi Itohara3, Takeo Yoshikawa2, Motomasa Tanaka1. 1Laboratory for Protein Conformation Diseases, RIKEN Brain Science Institute. 2Laboratory for Molecular Psychiatry, RIKEN Brain Science Institute. 3Laboratory for Behavioral Genetics, RIKEN Brain Science Institute. 4Laboroatory for Proteolytic Neuroscience, RIKEN Brain Science Institute. Many monogenic forms of autism spectrum disorder (ASD) are known to affect the mTOR signaling pathway, involving mutations in PTEN, TSC1, TSC2, and FMR1 genes. While recent work has focused on the dysregulation of protein translation via the deletion of these genes, few studies have examined how disruption of autophagy, another major downstream branch of mTOR signaling, contributes to neuronal dysfunction and ASD pathogenesis. To this end, we and others have previously examined mice deficient for autophagy in forebrain excitatory neurons via the deletion of Atg7 by CaMKII-cre and observed ASD-like behavioural abnormalities in addition to neuronal dysfunctions from the molecular to the network level. As ASD is believed to be caused by an imbalance between excitatory and inhibitory signals in the brain, we have further extended our analysis to examine disruption of autophagy in forebrain GABAergic interneurons. Similar to disrupted autophagy in other neuronal and non-neuronal cell types, Atg7 deletion by Dlx5-cre results in time-dependent ubiquitin+ and p62+ aggregate formation in affected neurons in the cerebral cortex, hippocampus, and striatum. Interestingly, with some minor differences, Dlx5-cre Atg7 cKO mice primarily exhibit a similar set of ASD-like behavioural abnormalities previously observed in CaMKII-cre Atg7 cKO animals. Furthermore, consistent with a specific defect on

GABAergic interneurons, we have detected a shift in the excitatory-inhibitory balance in the hippocampi of these knockout mice. Using primary neuron cultures, a reduction in the surface expression of GABAA receptor subunits was observed in Atg7 cKO neurons. Mass spectrometry and immunoblotting analyses of GABARAPL2, a member of the GABARAP (GABA receptor-associated protein) protein family, revealed that it accumulates in and shifts into the higher molecular weight fraction in both CaMKII-cre and Dlx5-cre Atg7 cKO brains. Knockdown of GABARAPL2 in wild-type primary neurons similarly showed reduced surface expression of GABAA receptors, thus suggesting that the loss of functional GABARAPL2 in Atg7 cKO neurons may be the causal link to the disruption of E-I balance and abnormal ASD-like behaviours observed in Atg7 cKO mice. K.H. was a recipient of the JSPS Postdoctoral Fellowship for Foreign Researchers and a member of the RIKEN Foreign Postdoctoral Researcher program.

CHD8 haploinsufficiency results in autistic-like phenotypes in mice. Yuta Katayama1), Masaaki Nishiyama1), Hirotaka Shoji2), Yasuyuki Ohkawa3), Atsuki Kawamura1), Tetsuya Sato4), Mikita Suyama4), Toru Takumi5), Tsuyoshi Miyakawa2) & Keiichi I. Nakayama1). 1) Department of Molecular and Cellular Biology, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan. 2) Division of Systems Medical Science, Institute for Comprehensive Medical Science, Fujita Health University, Aichi, Japan. 3) Division of Transcriptomics, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan. 4) Division of Bioinformatics, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan. 5) RIKEN Brain Science Institute, Wako, Saitam, Japan. Autism spectrum disorder (ASD) comprises a range of neurodevelopmental disorders characterized by deficits in social interaction and communication as well as by restricted and repetitive behaviours. ASD has a strong genetic component with high heritability. Exome sequencing analysis has recently identified many de novo mutations in a variety of genes in individuals with ASD, with CHD8 being most frequently affected. CHD8 is a member of the chromodomain helicase DNA-binding (CHD) family of proteins and functions as an ATP-dependent chromatin-remodeling factor in regulation of the expression of many genes including those for □-catenin and p53. However, whether CHD8 mutation is causative for ASD and how it might establish ASD traits have remained unknown. Here we show that mice heterozygous for Chd8 mutations manifest ASD-like behavioural characteristics including increased anxiety, persistence tendency, and altered social behaviour. Unexpectedly, transcriptome analyses revealed that CHD8 haploinsufficiency did not result in prominent changes in the expression of a few specific genes but rather gave rise to small but global changes in gene expression with neurodevelopmental delay in the mutant mouse embryos. Furthermore, reduced expression of CHD8 is associated with abnormal activation of RE-1 silencing transcription factor (REST), which suppresses the transcription of many neuronal genes. REST activation was also observed in the human ASD brain. Our results are thus consistent with the notion that CHD8 haploinsufficiency is a highly penetrant risk factor for ASD, with disease pathogenesis likely resulting from a delay in neurodevelopment.

Phenotypic analysis of a mouse model for 15q25.2-25.3 deletion syndrome. Jun Nomura1,2, Akifumi Kanda2, Jacob Ellegood3, Jason P. Lerch3, Yusuke Sotomaru2, Toru Takumi1,2. 1RIKEN Brain Science Institute, Wako, Japan, RIKEN, 2Graduate School of Biomedical & Health Sciences, Hiroshima University, Hiroshima, Japan,3Mouse Imaging Centre (MICe), The Hospital for Sick Children, Toronto, Canada. Human chromosome 15q25.2-25.3 deletion syndrome has been reported as one of the copy number variations associated with intellectual delay (ID) and mental retardation (MR) (Cooper et al., Nat. Genet., 2011). Patients with 15q25.2-25.3 (660 Kb, includes 7 genes, ZSCAN2, WDR73, NMB, ZNF592, ALPK3, SLC28A1, and PDE8A) microdeletion manifest variable clinical features, including mild motor delay, myopathy, mild

cognitive deficits, and ASD (autism spectrum disorder)-like symptoms. So far causal factors and mechanical evidences relevant to neuropsychiatric phenotypes have not been addressed. To analyze the consequence of 15q25.2-25.3 deletion, we have developed an animal model of human 15q25.2-25.3 heterozygous haploinsufficiency by chromosome engineering. Although this mutant mouse harboring 0.5 Mb deletion in chromosome 7 that corresponds to human 15q25.2-25.3 appeared normal and displayed no gross abnormalities so far, sequential behavioral analyses identified anxiety phenotypes in both open-field and elevated-plus maze tests. This mutant mouse also showed behavioral inflexibility in reversal learning test of Barnes maze although its hippocampal dependent spatial learning and memory tasks are normal. Furthermore, we performed brain imaging by applying 7-tesla Magnetic Resonance Imaging (MRI), and identified cerebellar cortex abnormalities in this mutant mouse. In this meeting, we report our progress of phenotypic analysis and discuss about its future perspectives.

13:30-15:30 **Symposium: Social stress on drug abuse vulnerability, cognitive function and aggressive behavior.** Chairs: Giovanni Biggio and Enrico Sanna. *Setouchi Hall, Room 1-2*

Methamphetamine addiction: activation of multiple stress pathways. Jean Lud Cadet, M.D. Molecular Neuropsychiatry Research Branch, NIDA Intramural Research Program, Baltimore, MD 21224. Methamphetamine (METH) addiction is a major public health problem throughout the world. METH addiction is accompanied by many psychiatric and neurological complications. These include cognitive deficits, psychosis, and movement disorders. To this date, there is no FDA-approved medication for the treatment of METH addition and therapies have been mostly behavioral. These have met with variable degrees of success. Animal models that use drug self-administration (SA) incorporate many features of human drug-taking behaviors. These rodent models have been very helpful in elucidating some of the mechanisms underlying METH addiction by deciphering its neurobiological substrates. This presentation will discuss a paradigm that helped to segregate rats that reduce or stop their METH intake (punishment-sensitive, PS) from those that continue to take the drug compulsively in the presence of footshocks (punishment-resistant, PS). We have used that model to investigate potential transcriptional alterations in the nucleus accumbens (NAc) because neuroplastic changes in the NAc may participate in the development and maintenance of drug-taking behaviors. We trained male Sprague-Dawley rats to self-administer methamphetamine (0.1 mg/kg/infusion) for 9 hours per day for 20 days. Control group self-administered saline. Subsequently, for methamphetamine self-administration rats, 50% of drug infusions were punished by mild electric footshock for 10 days, with shock intensity gradually increased over time. Two hours or 30 days after cessation of the last footshock and SA session, we euthanized the rats and isolated nucleus accumbens (NAc) samples from brains for further analysis. To investigate the role of stress pathways in METH SA, we measure the expression of the stress-related neuropeptide, corticotropin releasing hormone (CRH), and of its receptors, CRHR1 and CRHR2 in the NAc. We found significant increases in the expression of these genes in the NAc of all animals that were euthanized at 2 hours after SA. Measurements of vasopressin mRNA levels also revealed significant increases in its expression in the NAc. These observed increases in Crh and Avp mRNA levels suggest that METH exposure can lead to activation of multiple endogenous stress systems early in withdrawal. In contrast, we found significant increases in oxytocin only in the punishment-resistant (PR) rats. These findings suggest that pharmacological interventions that modulate stress responses in METH addiction may offer beneficial therapeutic approaches to METH-addicted patients.

Early life stress, increased alcohol intake and altered synaptic plasticity. Giuseppe Talani. Institute of Neuroscience, National Research Council, Cagliari, Italy. Traumatic eventsoccurring in early life may lead,in both humans and rodents,to a high risk for neuropsychiatric disorders as well as increased vulnerability to drug abuse in adulthood. Repeated maternal separation (RMS) in rodents is a useful model to investigate the consequences of neonatal stress on vulnerability to ethanol (EtOH) intake. In some cases, females are less affected by this stress paradigmsuggesting that sex hormones may play a pivotal role in protection.We here evaluated the potential mechanisms involved in the long-term effects of RMS on EtOH voluntary consumption in C57BL/6J adult mice and the changes in the function and plasticityof GABAergic and glutammatergicsynapses, in both hippocampus (Hip) and nucleus accumbens (NAcc).Male or female pups were separated daily from their dam for 360 min (from PND 2 to 17). RMS male mice showed a marked increase of EtOH intake and preference on the two-bottle free choice paradigm,while in females this result is not statistically relevant confirming a gender-dependent effect of RMS. Patch-clamp experiments revealed a significant enhancement in the tonic component of GABAergic inhibition recorded in dentate gyrus granule cells from RMS male mice compared with controls,while in females, RMS failed to induce similar changes.RMS is also accompanied with a marked increase in the frequency of GABAergic IPSCs recorded in the same neurons only in male animals compared to controls. Interestingly, all these changes were parallel byan impairment in LTD formation in the CA1 subregion of male RMS mice only, an effect paralleled by an impaired performance on the Barnes maze test. In the NAcc, we observed significant RMS-induced changes in synaptic plasticity when studied in GABAergic medium spiny neurons. Interestingly, preliminary experiments show that the RMS-induced impairments in synaptic plasticity as well as increasedEtOH consumption were no more appreciable when RMS male mice were treated with a single injection of beta-ethinylestradiol at PND3, suggesting that alteration in the hormonal asset strongly influences the action of RMS. Taken together, these findings demonstrate that RMS is associated long-lasting effects on synaptic plasticity in both hippocampus and NAcc of C57BL/6J male mice, a brain areas that are crucial in the control of learning and memory as well as goal directed behavior. Moreover, our data are in line with previous findings supporting a gender-dependent effect of RMS. Supported by CNR-DISVA-Sardegna Ricerche.

The relationship between stress, drug addiction and aggressive behavior. Giovanni Biggio1,2, Enrico Sanna1,2. 1University of Cagliari, Cagliari, Italy, 2Institute of Neuroscience, C.N.R., Cagliari, Italy. Increasing evidence from both pre-clinical and clinical studies demonstrates an association between stress and substance abuse and addiction. Stress not only plays a key role in influencing the development and expression of addictive behavior, but it is also a major cause of relapse following periods of abstinence in drug addicted subjects. In addition, early life (either in the neonatal period and during adolescence) environmental stress has been regarded as a risk factor for an increased vulnerability to develop psychiatric diseases, including depression, anxiety, and drug use disorders, as well as reduced cognitive function later in the adult life. Our present understanding of the link between early-life stress exposure and drug addiction later in the adult life is still limited and much research is needed in order to better clarify the neurobiological substrates that underlie this relationship. Thus, this symposium will include presentations that will discuss recent and exciting data that are emerging from drug of abuse-related studies that are using animal models of stress and applying multidisciplinary experimental protocols. Emphasis will be on the identification and characterization of novel pathophysiological and pharmacological mechanisms critical in addiction-related neuronal circuits that may be contributing to these stress-induced behavioral changes and, eventually, how these findings can be relevant for developing more selective and effective treatments for drug use disorders.

CRF-modulation in VTA-DRN escalates alcohol and cocaine intake after social stress. Klaus A. Miczek, Lara S. Hwa, Emily Newman, Herbert Covington III, Joseph F. DeBold. Departments of Psychology, Pharmacology, Psychiatry and Neuroscience, Tufts University, Medford and Boston, MA. Victims of aggression undergo neuroadaptive changes that escalate persistently alcohol- and cocaine self-administration in rodent models of drug abuse. CRF modulation of neural microcircuits comprising top-down control from the mPFC to VTA and DRN are candidate mechanisms for these long-lasting neuroadaptations. Our over-arching hypothesis examines the role of extra-hypothalamic CRF in victims of aggression who began to consume large amounts of cocaine and alcohol. Pharmacogenetic and optogenetic challenges and microdialysis measurements point to a critical role of CRF modulation of dopamine in the VTA. CFW and C57Bl/6J mice were given access to a 2-bottle choice protocol with 20% EtOH in one bottle every other day. Other mice were fitted with permanently indwelling intra-jugular catheters for self-administration of cocaine. Subgroups of animals were identified by their preference for EtOH and their high intake after they had experienced repeated episodes of social defeat stress. In further DREADD and optogenetic experiments, CRF processes surrounding DA cells within the posterior VTA were repeatedly stimulated in order to mimic salient features of social defeat stress in victims of aggression. Acute and repeated social defeat stress increased CRF and DA in the VTA. This increase in CRF is a candidate mechanism for subsequent escalation of EtOH consumption and cocaine "binges," given that CRF R1 and R2 antagonists can protect and reverse social stress effects. Activating the posterior VTA using either optogenetics or Gq-DREADD in CRF-Cre mice was sufficient to mimic chronic social defeat stress-induced drug-seeking behavior. These data reveal novel microcircuits for the escalation of aggressive behavior after consumption of acute doses of alcohol and after experiencing social defeat stress. We focus on the CRF cells in the DRN which modulate DA in the posterior VTA which in turn project to glutamatergic cells in the mPFC as targets for intervention.

16:00-16:30 **Early Career Achievement Award.** Sarah Baracz. *Setouchi Hall, Room 1-2*

Adolescent oxytocin treatment reverses the effects of early life stress on methamphetamine seeking behavior differently depending on sex. SarahBaracz[1,2], NickEverett[1], IainMcGregor[2], JenniferCornish[1]. [1]Macquarie University, NSW, Australia [2]University of Sydney, NSW, Australia. Exposure to early life stress is associated with augmented vulnerability to abuse illicit drugs, including the addictive psychostimulant methamphetamine (METH). Early life adversity also alters oxytocin regulation during one of the critical developmental periods of this important system. Such dysregulation contributes to increased susceptibility to developing drug dependence. Previous studies have shown that oxytocin pre-treatment during adolescence protects against future drug-taking and drug-seeking behaviour in animals without a history of early life stress. Considering this, the aim of our study was to determine whether an adolescent oxytocin treatment regime could reverse the adverse effects of early life stress and subsequently reduce susceptibility to METH dependence in adulthood. Long Evans pups were separated from their mothers for either 15 or 360 mins on postnatal days (PND) 1 to 21. During adolescence (PNDs 28-42), rats received a daily injection of either oxytocin (1mg/kg; ip) or saline. In adulthood, rats were instrumented for METH intravenous self-administration (IVSA). Rats acquired METH IVSA over 22 days (0.03mg/kg/infusion first 10 days, 0.1mg/kg/infusion final 12 days) after which they were exposed to extinction conditions. Following this, rats were exposed to drug-primed (0.3mg/kg and 1mg/kg; ip) and stress-induced reinstatement (yohimbine hydrochloride, 0.625mg/kg and 1.25mg/kg; ip) of METH-seeking behaviour. Our results showed that stressed female rats showed reduced reinstatement to METH-seeking behavior after exposure to a stressor (0.625mg/kg) when they received oxytocin during adolescence compared to

vehicle controls. Stressed male rats treated with oxytocin during adolescence showed a strong trend in the reduction of reinstatement responding after exposure to a METH-priming injection (1mg/kg) and a stressor (1.25mg/kg) when compared to stressed males who received vehicle injections. Overall, these findings suggest a role for adolescent oxytocin treatment in reducing the impact of early life stress on vulnerability to engage in drug-seeking behaviours, which differs depending on sex. This work was supported by a BSN PSG.

16:30-19:00 **Travel Award Data Blitz.** Chairs: Jill Silverman and Stacey Rizzo. *Setouchi Hall, Room 1-2*

Medial prefrontal cortex versus orbitofrontal cortex: teasing apart differences in plasticity after stress. Samantha Adler1, Sarah Bulin2, Michael Patton1, Milena Girotti1, David Morilak1. 1University of Texas Health San Antonio, San Antonio, TX, USA. Cognitive inflexibility is a symptom dimension shared by several stress-related psychiatric disorders; it contributes to their etiology and is exacerbated by stress, and yet it is poorly treated by current medications. To create better treatments, we need to know more about the neurobiology of stress effects on this symptom. In rodents, the attentional set-shifting task (AST) can be used to evaluate two types of cognitive flexibility: reversal learning, which is mediated by the orbitofrontal cortex (OFC), and extra-dimensional set-shifting, which is mediated by the medial prefrontal cortex (mPFC). We have identified two types of chronic stress that elicit deficits in each of these functions: chronic intermittent cold (CIC) stress impairs reversal learning ($p<.01$), while chronic unpredictable stress (CUS) impairs extra-dimensional set-shifting ($p<.05$). In recent work, we have found that each stress paradigm affects the output of the two brain regions very differently. Field potentials evoked acutely in the OFC by mediodorsothalamus (MDT) afferent stimulation in rats were potentiated after 2 weeks of CIC stress compared to baseline (before stress) ($p<.01$). Conversely, MDT-evoked responses in the mPFC were decreased after two weeks of CUS ($p<.001$). Since changes in excitatory transmission are often accompanied by morphological changes in dendrites, we are now analyzing the differences in dendritic arborization and spine density after stress by using Golgi staining. We expect stress-induced hyperactivity in the OFC to be associated with dendritic elaboration and increased spine density, and hypoactivity in the mPFC to be associated with dendritic retraction and decreased spine density. Finally, since changes in excitatory transmission correlate with altered AMPAR surface expression, we will also measure surface labeling of AMPAR subunits in the OFC and mPFC after chronic stress, anticipating that hyperactivity in the OFC is accompanied by increased AMPAR surface expression, while hypoactivity in the mPFC correlates with reduced AMPAR surface expression. This work was supported by NIMH grant R01 MH072672 and by a NIH Jointly Sponsored NIH Predoctoral Training Program in the Neurosciences training grant T32 NS082145.

Sexual behavior and pair bonding does not increase the number of new cells in the female and male prairie vole (Michrotus ochrogaster). Aguilar TE1, Diaz NF2, Young LJ3, Paredes RG1 and Portillo W1. 1 Instituto de Neurobiologia, UNAM. Mexico, 2Instituto Nacional de Perinatologia, Isidro Espinosa de los Reyes. Mexico and 3Emory University, Atlanta Georgia. USA. Pair bonding is a hallmark of social monogamy that is displayed by prairie voles (*Michrotus ochrogaster*) after 6 hrs of cohabitation with mating. Previous studies in rats and mice have shown that mating induces neurogenesis in olfactory bulb (OB) and dentate gyrus of hippocampus (DG). This effect has been demonstrated in the amygdala (AMG) and ventromedial hypothalamus (VMH) in (gonadally intact) female prairie vole following exposure to unfamiliar male. The current study further explores whether cohabitation with mating for 6 hrs induces neurogenesis. Forty eight voles (24 males and 24 females) were randomly assigned into three groups:

controls, social exposure and social cohabitation with mating. All females were ovariectomized and supplemented with estradiol during four days to induce sexual receptivity, males remained gonadal intact. In this paradigm, DNA synthesis marker 5-bromo-2- deoxyuridine (BrdU) was administrated 3 times every 2 hours to each group. Controls were isolated in different cages, while social exposure group remained in the same cage with a physical barrier, allowing odor and visual stimuli between female and male. The social cohabitation with mating group was recorded during 24 hours and the parameters of sexual behavior were determined. Fifteen days later voles were perfused and brain tissue was collected. Brain sections were processed for BrdU immunostaining. No differences in the number of new cells (BrdU+) were found in the AMG, VMH, granular and glomerular layer of the accessory and main OB and the medial preoptic area (PMA) between the groups in males and females. These results do not support a role for neurogenesis in pair bonding. This research was supported by grants CONACYT 252756, 167101; Fronteras 374; UNAM-DGAPA-PAPIIT IN203615, IN210215; Instituto Nacional de Perinatologia 212250-3230-21216-05-15 and Red Temática Células Troncales y Medicina Regenerativa. We thank Francisco Camacho, Deisy Gasca and Carlos Lozano for their technical assistance.

An altered neurodevelopmental profile in mice deficient for autism-associated Neurexin1 gene: communicative and motor aspects at an early stage. Caruso A1,2, Della Notte S 1, Fernandes C3, Scattoni ML4. 1 Center for Behavioral Sciences and Mental Health, Istituto Superiore di Sanità, Rome, Italy. 2 Doctoral School of Behavioral Neuroscience, Sapienza University of Rome, Italy. 3 Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK. 4 Research Coordination and Support Service, Istituto Superiore di Sanità, Rome, Italy. Autism Spectrum Disorders (ASD) are a group of behaviourally defined disorders characterized by abnormal social interactions and communication deficits, patterns of repetitive or stereotyped behaviours, as well as associated symptoms (e.g. motor alterations). Although the causes of ASD remain unclear, evidence strongly supports the role of genetic factors in their aetiology. Both common variations and rare mutations in the genes functioning at synapses in the brain have been identified in autistic patients, including Neurexin (NRXN) family genes. Our research has focused on mice with deletion of Nrxn1α gene encoding for a long isoform of neuronal presynaptic cell-adhesion molecules, with the main aim of investigating the behavioural consequences observed in absence of this gene. Specifically, our study has aimed the behavioural phenotyping of mice in order to identify one or more distinctive autistic-like features, as soon as possible during the early developmental period, since ASD are neurodevelopmental disorders with early onset of symptoms. We have evaluated the ontogentic profile of the vocal response during the first two weeks of life (postnatal day 2-12) through a detailed analysis of the ultrasonic vocalizations, by comparing Nrxn1α−/− null mutant, Nrxn1α+/− heterozygous and Nrxn1α+/+ wildtype littermate controls. Ultrasonic vocalizations are emitted by mouse pups in response to isolation from the mother and littermates and therefore considered a suitable tool for the identification of early communication deficits in autism mouse models. Moreover, since motor dysfunctions can predict the onset of the other symptoms in ASD, we have performed a fine-grain characterization of spontaneous motor behaviours, recorded simultaneously with the ultrasonic vocalizations. This is the first vocal and motor evaluation of Nrxn1α mutant pups that allows identification of autistic-like phenotypes at an early developmental stage, during which social deficits and other associated behavioural parameters often are difficult to identify. Our results indicate that an altered profile is detectable in the emission of ultrasonic vocalizations and acquisition of specific motor patterns in Nrxn1α mutant pups, in line with behavioural phenotypes observed in ASD children. Our findings suggest that the Nrxn1α gene has an important neurodevelopmental function and its deletion causes specific behavioural abnormalities, thus early deficits can be detected in this genetic model.

Reducing FKBP5 expression in the ventral hippocampus produces a PTSD-like phenotype without affecting anxiety or depressive-like behaviors. Marangelie Criado-Marrero1,2, Benjamín López-Torres1, César Torres Gutiérrez1, Anixa Hernández1, María Colón1, Ramón Misla David1, Chad A. Dickey2, James T. Porter1. 1Ponce Health Sciences University, Ponce, P.R.; 2University of South Florida, Tampa, FL. Despite the association of FK506 binding protein 5 (FKBP5) polymorphisms with post-traumatic stress disorder (PTSD), the mechanisms by which FKBP5 dysfunction can produce PTSD-like phenotypes is still unknown. Patients with PTSD have shown reduced FKBP5 gene expression in blood and impaired hippocampal activity. Since the hippocampus is sensitive to stress and FKBP5 impedes glucocorticoid receptor signaling, reduced FKBP5 expression could facilitate the formation of long-lasting traumatic memories by allowing enhanced glucocorticoid receptor activity. Thereby, we hypothesized that the uncontrolled fear response after trauma may be due to hippocampal malfunction as a consequence of low levels of FKBP5. To test this, we examine the baseline FKBP5 protein levels in ventral hippocampus (VH) and blood in adult male rats, and then compare expression changes after fear conditioning and extinction. We found that FKBP5 was reduced in VH after fear conditioning and this protein reduction was negative correlated with conditioned fear expression suggesting that less expression of FKBP5 protein in VH might facilitate the acquisition of conditioned fear. Next, we assessed whether reducing FKBP5 protein in VH is sufficient to alter fear conditioning. We infused into the rat's brain a FKBP5 shRNA plasmid to reduce FKBP5 protein and waited 5 days before exposing to behavioral test. By lowering FKBP5 in VH, our rats showed a PTSD-like phenotype with enhanced fear acquisition during fear conditioning and fear extinction recall. We further observed that the c-fos expression in VH was significantly increased in rats infused with FKBP5-shRNA compared to control infused rats indicating that reducing FKBP5 increases VH activity. To eliminate the possibility that reducing FKBP5 in VH enhances freezing behavior during auditory fear conditioning by reducing locomotion or increasing anxiety-like or depression-like behaviors, we exposed separate groups to open field, elevated zero maze, and force swimming tests five days after infusion of FKBP5-shRNA plasmid in VH. Our results confirmed that reducing VH FKBP5 affects fear conditioning and extinction without affecting locomotion, anxiety-like, or depression-like behaviors. Our findings extend other studies showing changes in VH FKBP5 activity as we directly demonstrate that modulating FKBP5 in this structure affects fear learning, as it may be also happening in patients with PTSD. Thus, future studies should be directed to describe the molecular mechanism by which FKBP5 modulates fear expression in the VH. This project is supported by the RCMI Behavioral and Molecular Biology Core Labs (Grant 8G12MD007579), R15 MH101700, RISE Program (Grant R25GM082406), and Diversity Supplement NS073899 (Dickey/Criado-Marrero) from the National Institutes of Health.

Comparing the antidepressant efficacy of voluntary running and fluoxetine in a rat model of postpartum depression: effects on maternal care, depressive-like behavior, and hippocampal neurogenesis. Gobinath, A.R.1, Richardson, R.J.2, Chow, C2, Workman, J.L.2, Lieblich, S.E.2, Barr, A.M.3, Galea, L.A.M1,2. 1Program in Neuroscience, University of British Columbia, 2Department of Psychology, University of British Columbia, 3Department of Anesthesiology, Pharmacology, and Therapeutics, University of British Columbia. Postpartum depression (PPD) affects approximately 15% of mothers and imposes a lifelong burden of mental health concerns for women. Pharmacological antidepressants such as fluoxetine (Prozac) are commonly used to treat PPD. However, use of fluoxetine during the postpartum period remains controversial due to concerns of efficacy as well as neonatal exposure to the drug. For this reason, non-pharmacological therapies such as exercise may be of interest as an alternative intervention. However, physiological changes that are characteristic of the postpartum period may alter the antidepressant potential of exercise and/or SSRIs (selective serotonin reuptake inhibitors). To investigate

this, we treated rat dams daily with high levels of corticosterone (40 mg/kg), to induce a depressive-like phenotype, or oil during the postpartum period. Within the oil and corticosterone conditions, four additional antidepressant groups were created: 1. Fluoxetine (Prozac; 10 mg/kg) + exercise (voluntary access to running wheel); 2. Fluoxetine + no exercise; 3. Saline (vehicle for fluoxetine) + exercise; 4. Saline + No exercise. Dams were tested for alterations in maternal behavior and depressive-like behavior (forced swim test). We also quantified serum corticosterone levels as well as doublecortin (marker of immature neurons) expression in dorsal and ventral dentate gyrus. Daily running activity was recorded and using a median split, dams were further categorized as "high-running" or "low-running." Preliminary results reveal that maternal fluoxetine reversed corticosterone-induced disruptions in maternal care, especially in low-running but not high-running dams. Exercise also tended to decrease immobility (depressive-like behavior) in the forced swim test. The combination of exercise and fluoxetine attenuated stress-induced rises in serum corticosterone in comparison to fluoxetine alone. Finally, exercise bolstered doublecortin expression in ventral but not dorsal dentate gyrus in comparison to non-exercising dams. Of corticosterone-treated dams, the combination of high-running and fluoxetine increased doublecortin expression in ventral dentate gyrus in comparison to fluoxetine alone. Our findings show that maternal antidepressant treatments (Prozac, exercise) interact to differentially affect the well-being of the mother at the behavioral, endocrine, and hippocampal levels. Funded by CIHR to LAMG.

Basolateral amygdala and anterior cingulate contributions to effortful choice behavior. Evan E Hart1, Julian Gerson1, Yael Zoken1, Marisella Garcia1, Alicia Izquierdo1. 1University of California, Los Angeles. The basolateral amygdala (BLA) and anterior cingulate cortex (ACC) are known to be involved in appetitive behavior, yet their role in cost-benefit choice of qualitatively different rewards (more/less preferred), beyond magnitude differences (larger/smaller), is poorly understood. We assessed the roles of BLA and ACC on effortful choice. Rats were surgically prepared with either cannulae in BLA or NMDA lesions of ACC and trained to stable lever pressing for sucrose pellets on a progressive ratio schedule. Rats were then introduced to a choice: freely-available chow was concurrently available while they could work for the preferred sucrose pellets. Rats in the BLA experiment were infused with either vehicle control (aCSF) or baclofen/muscimol prior to test. BLA inactivations produced a decrease in lever presses for sucrose pellets compared to vehicle, and chow consumption was unaffected. Inactivation had no effect on sucrose pellet preference when both options were freely available. Critically, when lab chow was not concurrently-available, BLA inactivations had no effect on the number of lever presses for sucrose, indicating that primary motivation in the absence of choice remains intact with BLA offline. During a test under specific satiety for sucrose pellets, BLA inactivation rendered animals less sensitive to devaluation relative to control. The effects of BLA inactivations in our task are not mediated by decreased appetite, an inability to perform the task, a change in food preference, or decrements in primary motivation. Similar to BLA inactivation, ACC lesions produced a significant decrease in lever presses for sucrose pellets compared to sham-operated rats (SHAM), and chow consumption was unaffected. Also like BLA inactivations, ACC lesions had no effect on sucrose pellet preference when both options were freely-available. However, in contrast to our BLA findings, when lab chow was not concurrently available ACC lesions reduced the number of lever presses for sucrose pellets. During a test under specific satiety for sucrose pellets, ACC lesions had no effect on response to devaluation relative to SHAM. The effects of ACC lesions are not mediated by decreased appetite, a change in food preference, or changes in value of the preferred reward, and instead may be due to general work aversion. Taken together, BLA supports the specific value and effortful choice of a preferred option, and the ACC supports willingness to exert effort generally. This

work was supported by UCLA's Division of Life Sciences Recruitment and Retention Fund (Izquierdo) and NIH T32DA024635-08 (Hart).

Disruption of autophagic signaling in murine forebrain affects excitatory-inhibitory balance via mistrafficking of GABAA receptors leading to ASD-like behaviours. Kelvin Hui1, Noriko Takashima1, Hiroshi Matsukawa1,3, Akiko Watanabe2, Per Nilsson4, Ryo Endo1, Takaomi Saido4, Shigeyoshi Itohara3, Takeo Yoshikawa2, Motomasa Tanaka1. 1Laboratory for Protein Conformation Diseases, RIKEN Brain Science Institute. 2Laboratory for Molecular Psychiatry, RIKEN Brain Science Institute. 3Laboratory for Behavioral Genetics, RIKEN Brain Science Institute. 4Laboroatory for Proteolytic Neuroscience, RIKEN Brain Science Institute. Many monogenic forms of autism spectrum disorder (ASD) are known to affect the mTOR signaling pathway, involving mutations in PTEN, TSC1, TSC2, and FMR1 genes. While recent work has focused on the dysregulation of protein translation via the deletion of these genes, few studies have examined how disruption of autophagy, another major downstream branch of mTOR signaling, contributes to neuronal dysfunction and ASD pathogenesis. To this end, we and others have previously examined mice deficient for autophagy in forebrain excitatory neurons via the deletion of Atg7 by CaMKII-cre and observed ASD-like behavioural abnormalities in addition to neuronal dysfunctions from the molecular to the network level. As ASD is believed to be caused by an imbalance between excitatory and inhibitory signals in the brain, we have further extended our analysis to examine disruption of autophagy in forebrain GABAergic interneurons. Similar to disrupted autophagy in other neuronal and non-neuronal cell types, Atg7 deletion by Dlx5-cre results in time-dependent ubiquitin+ and p62+ aggregate formation in affected neurons in the cerebral cortex, hippocampus, and striatum. Interestingly, with some minor differences, Dlx5-cre Atg7 cKO mice primarily exhibit a similar set of ASD-like behavioural abnormalities previously observed in CaMKII-cre Atg7 cKO animals. Furthermore, consistent with a specific defect on GABAergic interneurons, we have detected a shift in the excitatory-inhibitory balance in the hippocampi of these knockout mice. Using primary neuron cultures, a reduction in the surface expression of GABAA receptor subunits was observed in Atg7 cKO neurons. Mass spectrometry and immunoblotting analyses of GABARAPL2, a member of the GABARAP (GABA receptor-associated protein) protein family, revealed that it accumulates in and shifts into the higher molecular weight fraction in both CaMKII-cre and Dlx5-cre Atg7 cKO brains. Knockdown of GABARAPL2 in wild-type primary neurons similarly showed reduced surface expression of GABAA receptors, thus suggesting that the loss of functional GABARAPL2 in Atg7 cKO neurons may be the causal link to the disruption of E-I balance and abnormal ASD-like behaviours observed in Atg7 cKO mice. K.H. was a recipient of the JSPS Postdoctoral Fellowship for Foreign Researchers and a member of the RIKEN Foreign Postdoctoral Researcher program.

Coordination of orofacial motor actions with respiration in the rat during ingestive, exploratory, and foraging behaviors. Song-Mao Liao1, Hiteshwar Rao2, David Kleinfeld1,3,4. 1Department of Physics, University of California, San Diego, La Jolla, CA 92093, USA, 2Department of Bioengineering, University of California, San Diego, La Jolla, CA 92093, USA, 3Section of Neurobiology, University of California, San Diego, La Jolla, CA 92093, USA, 4Department of Electrical and Computer Engineering, University of California, San Diego, La Jolla, CA 92093, USA. Rodents perform orofacial motor behaviors, which include sniffing, whisking, head bobbing, licking, chewing, nose twitching, and vocalizing, as a means to sample their peripersonal space as well as to ingest nutriments. The motor actions must be exquisitely coordinated, not only to efficiently execute environmental sampling routines but also to maintain the patency of the upper airway. Here we address the nature of this coordination to shed light on the neuronal connectivity among the different premotor central pattern generators that are embedded in the brainstem and orchestrate the rhythmic motor outputs. We record the ingestive and exploratory behaviors of rats with microelectronic sensors and videography, along with the electromyogram (EMG) of

the underlying muscles and the concurrent respiration. We found that the exploratory head-bobbing is phase-locked with sniffing. The onset of inspiration drives a sampling cycle of the peripersonal space; this involves movement of the head, along with the vibrissae and nose, that is phase-locked to breathing. In ongoing work, we found that the tongue and jaw movements are phase-locked to each other and to breathing during licking. The licking rate is paced near 7 Hz, while the ratio of the licking cycles to the breathing cycles forms a discrete and breathing-dependent temporal pattern. The chewing rhythm is paced near 6 Hz and the tongue will preferentially phase-lock to chewing over breathing. No temporal relationship between chewing and breathing is observed, consistent with two independent brainstem oscillators in orofacial control. We are extending this approach to study the coordination of orofacial motor actions with respiration cycles during exploratory and foraging behaviors performed by the rat in an open field. Supported by US NIH grants NS0905905 and NS058668, US NSF EAGER grant 2144GA, and the Taiwan Studying Abroad Scholarship to S.-M. L.

Cortical-amygdala circuits for value-based decision making. Melissa Malvaez1, Christine Shieh1, Michael Murphy1, Venuz Y. Greenfield1, Harold G. Monbouquette3, and Kate M. Wassum1,2. 1. Dept. of Psychology, UCLA, Los Angeles, CA 90095. 2. Brain Research Institute, UCLA, Los Angeles, CA 90095, USA. 3. Dept. of Chemical Engineering, UCLA, Los Angeles, CA 90095, USA. The value of an anticipated reward is a major contributing factor in the decision to engage in actions towards its pursuit. Such value is dynamic, fluctuating based on one's current need state, and must be learned through relevant state experience (e.g., consumption of a food item while hungry). The basolateral amygdala (BLA) is required for this incentive learning process, but little is known about how it achieves this function within the broader reward-seeking circuitry and whether it also participates in the online use of reward value during decision making. Because the BLA is densely innervated by cortical glutamatergic projections, we hypothesized that glutamate released into the BLA would track changes in reward value important for value-guided reward seeking. To test this, we used electroenzymatic biosensors to make near-real time measurements of BLA glutamate concentration changes during incentive learning (experience with a food reward in novel hungry state) and a subsequent reward-seeking test. Transient elevations in BLA glutamate concentration were detected that tracked the incentive learning process. No such changes were detected in the absence of incentive learning when the food was experienced in a familiar state. BLA glutamate elevations were also detected immediately preceding bouts of subsequent reward-seeking activity, but only if rats had access to the current value of the food reward. Supporting these correlational data, inactivation of BLA NMDA glutamate receptors prevented incentive learning, while inactivation of either BLA AMPA or NMDA receptors attenuated the normal increase in reward seeking that would occur following a positive incentive learning opportunity. We next used designer receptor-mediated inactivation of specific glutamatergic cortical projections to the BLA to determine the afferent contributors to these input signals. Projections from the lateral orbitofrontal cortex (OFC) were found to be necessary for encoding a positive change in reward value, but not for later retrieval of this information for online decision making. Conversely, projections from the medial OFC were not required for incentive learning, but their inactivation did disrupt online reward-seeking activity. These data demonstrate that the BLA participates in both the encoding and retrieval reward value via input signals from the lateral and medial OFC, respectively. NRSA 1F32DA038942. TNDA 5T32DA024635. R01-DA035443.

Ventral tegmental area-Cav1.3 L-type Ca 2+ channels CaMKII/ERK2/CREB signaling is essential for long-term adaptation in AMPARs in the nucleus accumbens. A. Martinez-Rivera [1, 2] , Thomas Giordano[1] , Gagan Kaur1 , Joerg Striessnig[3,4] , Nii Addy[5] , Anjali M. Rajadhyaksha[1, 2], [1]Department of Pediatrics, Division of

Pediatric Neurology, New York Presbyterian Hospital, [2]Feil Family Brain and Mind Research Institute, Weill Cornell Medical College, NY, NY, [3]Pharmacology and Toxicology, University of Innsbruck, [4]Center for Molecular Biosciences, University of Innsbruck, Innsbruck, Austria, [5]Department of Psychiatry and Department of Cellular and Molecular Physiology, Yale School of Medicine, New Haven, CT, USA; Interdepartmental Neuroscience Program, Yale Graduate School of Arts and Science, New Haven, CT, USA. Human genetic studies have linked the L-type calcium channel (LTCC) genes to multiple neuropsychiatric disorders. In particular, the CACNA1D gene that codes for the $Ca_v1.3$ subunit of LTCCs has been associated with bipolar disorder (BP) and cocaine dependence, highly co-morbid conditions and we recently demonstrated that $Ca_v1.3$ channels within the ventral tegmental area (VTA) to nucleus accumbens (NAc) pathway plays a critical role in cocaine-and depressive-like behavior, highlighting the importance of this gene and channel. However, the molecular mechanisms within the VTA that mediate the cocaine and depressive-like behaviors are still unknown. In the present study, using mutant mice expressing 1,4 dihydropyridines (DHP)-insensitive $Ca_v1.2$ ($Ca_v1.2DHP^{-/-}$) we find that the LTCC blocker nifedipine that specifically targets $Ca_v1.3$ channels in these mice, inhibits cocaine-induced phosphorylation of CaMKIIalpha, ERK, and CREB within the VTA and GluA1 within the NAc. To directly map the $Ca_v1.3$ Ca^{2+} signaling mechanisms that underlie cocaine seeking behavior we utilized cocaine conditioned place preference (CPP). Blockade of CaMKII in the VTA by utilizing KN93 (CaM kinase II inhibitor) before each cocaine conditioning session, attenuated cocaine CPP and cocaineinduced CREB, and ERK phosphorylation, and cocaine-induced GluA1 higher levels within the NAc. Furthermore, blockade of ERK with the ERK inhibitor U0126 or ERK2 siRNA, attenuated cocaine CPP, VTA-CREB phosphorylation and NAc-GluA1, but not VTA-CaMKIIalpha phosphorylation, suggesting that ERK is activated downstream of CaMKIIalpha that then activates CREB. To further explore the neurotransmitter mechanisms that are recruited upstream of VTA $Ca_v1.3$ channels we are currently exploring the laterodorsal tegemental nucleus (LDTg) that sends glutamatergic, GABAergic and cholinergic projections to the VTA and a projection shown to be sufficient to induce place preference. Our preliminary results using chemogenetic DREADD manipulations demonstrate that inhibition of the LDTg, with hM4Di-DREADD blocked cocaine CPP. However, inhibiting glutamatergic LDTg projections had no effect on cocaine CPP, suggesting a potential role of LDTg cholinergic or GABAergic mechanisms in driving cocaine CPP. Taken together, our findings demonstrate that VTA Cav1.3 channel signaling mechanisms are necessary for cocaine place preference and may recruit the LDTg-VTA pathway.

The effects of blocking nucleus accumbens dopamine D1-type receptors on social learning of food preferences in male and female mice. Richard Matta1, Madison J. Russell1, Danielle J. Tessier1, and Elena Choleris1. 1Department of Psychology and Neuroscience Program, University of Guelph, Guelph, ON, Canada, N1G2W1. The neurotransmitter dopamine (DA) is involved in the regulation of numerous motivationally relevant behaviors, including drug-addiction, feeding, and social behavior. Previous work in our lab using systemic treatments has implicated D1-type (D1/D5) DA receptors in social learning and D2-type (D2/D3/D4) DA receptors in feeding behavior in the social transmission of food preferences (STFP) in mice (Choleris et al, 2011). The underlying brain region(s) of action mediating these effects are slowing being investigated. The ventral tegmental area has direct dopaminergic projections to many limbic brain regions, including the hippocampus and nucleus accumbens (NAc). Our previous studies using D1-type and D2-type DA receptor antagonists has shown that dorsal hippocampal D1-type and D2-type DA receptors mediate social learning in female mice, whereas only dorsal hippocampal D1-type receptors mediate social learning in males (Matta et al, 2014, 2016). NAc D1-type DA receptors have been strongly implicated in both social behaviours, and in individually acquired food preferences in rodents. Hence, the purpose of this study was to investigate the role of NAc D1-type DA receptors in the STFP in male and female mice. To do this, we microinfused the D1-type DA receptor antagonist SCH23390 (at 1, 2, and 4

μg/μL) directly into the NAc shell of adult male and female CD-1 mice. NAc infusions were 15 minutes before a 30 minute social interaction where mice had the opportunity to learn a food preference from a recently fed same-sex conspecific. Initial results show that the highest dose of SCH23390, at 4 μg/μL, blocked social learning. Furthermore, this social learning impairment could not be explained by any generalized changes in feeding behavior, since drug treatment did not affect total food intake. These results are consistent with those of our previous work using systemic treatments, and our intrahippocampal studies showing that D1-type DA receptors mediate social learning in the STFP. This study suggests that NAc D1-type DA receptors may also be regulating social learning in mice. Throughout, we will be highlighting sex differences, and possible effects of the estrous cycle on social learning. Supported by NSERC.

Correlation between psychostimulant-induced alterations of local field potentials within primary visual circuits and improved performance of a sensory signal detection task. Rachel L. Navarra1,2, Brian D. Clark1,2, Barry D. Waterhouse1,2. 1Rowan University School of Medicine, 2Drexel University College of Medicine. Methylphenidate (MPH) is a psychostimulant used clinically to treat attention deficit hyperactivity disorder (ADHD) and off-label as a performance enhancing drug by healthy individuals. MPH enhances catecholamine transmission via blockade of norepinephrine and dopamine transporters, but how this action impacts neural circuits responsible for cognitive and sensorimotor functions to improve performance is unclear. We previously reported that MPH enhances neuronal responses to visual stimuli within the rat dorsal lateral geniculate nucleus (dLGN) while improving the speed to make correct responses during performance of a visual signal detection task. Here, we investigated a range of MPH effects on behavioral outcomes and measures of local field potentials (LFPs) in the dLGN during performance of the task. P30, the first positive deflection of the visual evoked potential (VEP) produced in response to task-related visual stimuli, was reduced in latency and amplitude following MPH administration. Across animals there was a significant positive correlation between P30 latency and latency to make correct responses, where the fastest times were found with MPH. Further, MPH increased coherence between LFPs at theta frequencies, which have been linked to variations in cognitive and sensorimotor processes. Thus, it appears MPH speeds, strengthens, and better integrates signals within the dLGN; effects that are consistent with faster sensory signal processing and better visual signal detection. To our knowledge this is the first demonstration of a direct correlation between electrophysiological measures of sensory processing in a primary thalamic relay circuit and behavioral outcomes in a visual signal detection task. These results have led to the generation of a theoretical model in which MPH manipulates noradrenergic mechanisms to create optimal conditions for enhanced processing of sensory information. Sensory information is then transmitted to decision making circuits with greater speed and strength to result in more efficient behavioral responses. This work suggests that MPH-induced sensory enhancement may be a significant component of psychostimulant-mediated performance enhancement in ADHD patients and healthy individuals. Funding support: PhRMA Foundation Pre-Doctoral Award (Rachel Navarra), NIH/NIDA NRSA F31DA037651 (Rachel Navarra), NIH/NIDA R01 DA017960 (Barry Waterhouse, PI).

Embracing nature's social network: The effect of an engaging environment on social responsiveness and oxytocin-immunoreactivity. Neal, S.1, Kent, M.1, Bardi, M.1, Scarola, S.1, Perdomo, J.1, Thompson, B., Lambert, S.2, Lambert, K3. 1Randolph-Macon College, 2Furman University, 3Universty of Richmond. In contemporary society, there is an increased use of virtual reality in which humans are spending an inordinate amount of time interacting with screens as opposed to more naturalistic physical

environmental stimuli consistent with the experiences of our ancestors. In 2016, for example, Facebook reported 1.5 billion monthly active users. Further, with the increased use of social media platforms, actual social interaction and engagement are also diminishing. Accordingly, in the current study, the effect of varying levels of environmental engagement on social responsiveness was investigated. Specifically, male Long-Evans rats were exposed to one of three environments: 1) group-housed in a naturally enriched environment (EE), 2) group-housed in a standard laboratory environment, or 3) housed in isolation in a standard laboratory environment (n=8). Previous work in the Randolph-Macon Behavioral Neuroscience Laboratory indicated that natural-enriched habitats promoted more social engagement than the artificial-enriched environment; thus, the natural-enriched environment was used. During the 4 weeks of assigned habitat exposure, spontaneous behavior was observed for 1 hour during the dark period for the social-housed groups. Also, each rat was assessed in a social responsiveness task. Following behavioral assessments, animals were perfused and brains were processed for oxytocin (OT) immunoreactivity in the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus and the medial forebrain bundle (MFB). Results indicated that, during dark-phase spontaneous behavioral observations, rats housed in EE displayed significantly higher rates of affiliative social behavior (i.e., active social contact, inter-male grooming and rough-and-tumble play) than the standard group-housed animals ($p=0.001$). However, higher rates of self-focused behavior (i.e., self-grooming) were observed in the standard group-housed rats ($p=0.03$). In the social responsiveness task, rats in EE directed more attention toward the novel conspecific in a restraint tube than the other two groups. For example, EE animals exhibited longer periods of sniffing bouts directed towards novel conspecific than the control ($p=0.006$). Results from neural quantification of OT-immunoreactivity indicated higher immunoreactive areas in the SON, but not in the PVN or the MFB, in the EE group ($p=0.04$). These findings suggest that environments promoting affiliative behavior enhance the responsiveness to novel conspecifics, potentially mediated by altered OT responsivity.

Persistent effects of acute stress on fear and drug-seeking in a novel model of the comorbidity between post-traumatic stress disorder and addiction. Pizzimenti, Christie L1; Navis, Thomas M1 & Lattal, Matthew K1. 1Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, OR USA. Fear-related disorders and substance use disorders are highly comorbid. Even following long periods of abstinence, comorbid individuals have high rates of relapse to drugs of abuse, especially in response to cues previously paired with drug. Previous attempts to characterize the role of fear on reinstatement have administered both the drug and the stressor within the same environment. Therefore, little is known about how fearful experiences in a specific context cause persistent changes in drug-seeking behavior in other contexts. To address this we assessed the effects of massive footshock in one context on drug seeking in another context using intravenous self-administration of methamphetamine in rats and cocaine-induced conditioned place preference in mice. Hyper-responsiveness to a mild stressor was assessed using a stress-enhanced fear learning procedure. Plasma levels of corticosterone (CORT) following footshock as well as following a dexamethasone (DEX) test were assessed using a radioimmunoassay to determine the role of hypothalamic-pituitary-adrenal (HPA) dysfunction in long-term stress effects. Mice with a history of footshock in a distinct context showed a significantly enhanced cocaine-induced place preference. In addition, massive footshock in a distinct environment produced long-term enhancements in cue-induced reinstatement of drug-seeking behavior in rats. These animals were also resistant to extinction following reinstatement. Although massive footshock produced an acute increase in CORT this change did not persist over time, consistent with reports in humans with post-

traumatic stress disorder that cortisol levels are not chronically elevated. These studies demonstrate that a history of acute trauma leads to persistent changes in fear and drug-seeking behavior in other contexts, which mirrors aspects of the comorbidity between post-traumatic stress disorder and substance use disorders. These behavioral approaches provide a novel procedure for investigating basic mechanisms underlying this comorbidity and they provide powerful tools for testing preclinical pharmacological and behavioral interventions.

Time-restricted feeding exerts anti-inflammatory and neuroprotective effects on acute seizure model. Santillan-Cigales, Juan Jair [1]; Landgrave-Gomez Jorge[1]; Mercado-Gomez Octavio Fabian[1]; Guevara-Guzman, Rosalinda[1]. [1]Universidad Nacional Autonoma de Mexico. During the past decade, experimental research has demonstrated a prominent role of the pro-inflammatory molecules on epileptogenic and ictogenic processes. On the other hand, our research group recently demonstrated that time- restricted feeding (TRF) had an anticonvulsant effect, however, the precise mechanism by which this diet exerts its beneficial effects are still unknown. Our aim was to investigate whether TRF is able to exert its beneficial effect decreasing the expression of pro-inflammatory molecules and thus might have a neuroprotective role after seizure induction. Briefly, TRF consisted in allowing rats to eat for two hours daily during their light phase for 20 days; conversely, control group was fed *ad libitum* (AL). After dietary schedule, *status epilepticus* (SE) was induced using a pre-treatment with a injection of lithium chloride (3 mEq/kg) followed by pilocarpine administration (60 mg/kg).Both protein and mRNA expression of pro-inflammatory molecules such as interleukin 1 beta (IL-β), tumor necrosis factor alpha (TNF-á) and interleukin 6 (IL-6) were measured in hippocampus from each group 24 h after SE. Additionally, coronal brain slices were processed with fluoro-Jade C to mark degenerate neurons. Our preliminary data showed that the group that followed TRF before SE had a significant decrease in both of mRNA and protein expression of pro-inflammatory molecules (IL-β, TNF-á, IL-6), in comparison with AL group after seizure induction. Furthermore, the hippocampus from TRF group showed a significant decrease on reactive gliosis and less FluroJade-positive cells were observed after SE. Our data demonstrate that TRF may exert a neuroprotective effect by decreasing the mRNA and protein expression of pro-inflammatory molecules and reactive gliosis after seizure induction.

Effects of preconceptional corticosterone and prenatal antidepressant treatment on stress, responsivity and hippocampal neurogenesis in the next (F2) generation. Abdul-Rahman Suleiman1, Susanne Brummelte1. 1Department of Psychology, Wayne State University, Detroit, MI 48202. The study was designed to investigate the effects of preconceptional maternal depression and gestational antidepressant treatment on the second generation. High levels of the stress hormone corticosterone (40 mg/kg) were given to female rats for 21 days before pregnancy to induce depressive-like behavior. Corticosterone-treated or healthy female rats (F0 generation) received sertraline (a selective serotonin reuptake inhibitor; 20mg/kg) or vehicle via oral gavage ~5 days prior to mating and continued the treatment until end of gestation. Female F1 offspring were mated with naïve males to produce the F2 generation. Adolescent male and female F2 rats were tested in several behavioral tests before being sacrificed and the brains extracted and processed for doublecortin (DCX) staining for immature neurons. Results suggest transgenerational effect of corticosterone exposure on the F2 litter weights but no strong effect on the adult behavioral outcome in the Forced Swim Test for depressive-like behavior or the Open Field Test for anxiety-like behavior. We hypothesize to see altered stress responses to the Restraint Stress Test in F2 offspring from F0 dams that received corticosterone and reduced levels of hippocampal

neurogenesis. Our results will illuminate the potential transgenerational effects of maternal depression and antidepressant treatment for future generations.

TRPV1 receptor modulates different phases of conditioned fear learning. Ana Luisa Terzian; Leonardo BM Resstel. School of Medicine of Ribeirão Preto. University of São Paulo, Brazil. TRPV1 receptor (rTRPV1; transient receptor potential vanilloid type 1) is widely distributed in the central nervous system (CNS), on areas involved with modulation of emotional responses such as midbrain and prefrontal cortex. Pharmacological or genetic inhibition of this receptor reduces neuronal activity, resulting in decreased fear and anxiety levels. However, few studies investigated the role of rTRPV1 on different phases of acquired fear, which is highly related to species survival and several psychiatric disorders. Therefore, this study aimed to investigate the role of rTRPV1 in different phases of cued fear conditioned (CFC) in wild-type (WT) and rTRPV1 knockout mice (TRPV1-/-). Mice (WT or TRPV1-/-; C57bl/6 background; 8-12 weeks) were submitted to the 3-days CFC protocol. On the first day (d0), animals received foot-shock associated with an auditory cue in context A [5 shocks, 0,65mA, 1s; paired with a tone (30s, 1kHz, 70dB)]. Twenty-four hours later (d1), animals were placed in a different context B, where the auditory cue was presented without foot-shock. On the third day (d2), animals were submitted to the same conditions as in d1. The fear acquisition (d0), extinction (d1) and extinction learning (d2) were evaluated based on the level of freezing behavior. WT mice implanted with guide cannula into the medial prefrontal cortex received microinjection of TRPV1 antagonist 6-iodonordihydrocapsaicin (6-iodo; 3-10nmol/100nL) or vehicle. Microinjections were performed either pre-d1, post-d1, or pre-d2. On CFC protocol, the cued fear acquisition was similar for all groups tested. Nonetheless, on the following days (d1-d2) TRPV1-/- showed reduced freezing behavior, resulting in improved extinction learning when compared to control. TRPV1 antagonist 6-iodo reduced fear expression in d2, independent of injection time, suggesting a long-lasting effect after receptor blockade. In conclusion, our results suggest rTRPV1 involvement in the modulation of learned behaviors with emotional content, indicating a prospective treatment for several psychiatric disorders. Financial support: FAPESP, CAPES, CNPq, IBRO, IBNS.

Adult hippocampal neurogenesis affects behavioral responses to an operant model of frustrative nonreward. Mumeko C Tsuda, Rose-Marie Karlsson, and Heather A Cameron. Section on Neuroplasticity, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA. A common characteristic of several psychiatric disorders is irritability, which is defined as aberrant responses to frustration, or the absence of an expected reward. The hippocampus has been implicated in response to frustration. The present study investigated the role of adult hippocampal neurogenesis in behavioral responses to frustration induced by loss of an expected reward. We used valganciclovir to inhibit adult neurogenesis in male mice expressing the herpes simplex virus thymidine kinase (TK) under a GFAP promoter. Both TK and wild-type (WT) littermate controls were mildly food restricted and trained in operant chambers to lever press for food tablets on fixed ratio (FR) schedule where a light cue above the lever was paired with the reward. A progressive ratio (PR) test followed FR, and mice that reached 150 lever presses in the PR either received (rewarded group) or did not receive (frustrated group) a reward. Mice in both groups were shown the light cue associated with reward. After the PR, mice remained in the operant box for an additional 10 min where lever pressing had no scheduled consequence. Immediately after the 10 min period, mice were tested in the resident-intruder test of aggression. A negative control group spent time in the operant chamber but did not receive light cues or rewards during FR and PR. WT mice exposed to the frustration condition showed greater lever pressing and greater aggression relative to rewarded mice. Frustrated TK mice showed even greater lever pressing than WT mice in the same

condition but showed baseline levels of aggression. These results suggest that adult hippocampal neurogenesis affects behavioral responses to frustration induced by the loss of an expected reward.

Central amygdala relaxin-3/rxfp3 signalling modulates alcohol-seeking in rats. Leigh C Walker1,2, Hanna E Kastman1,2, Elena Krstew1,2, Andrew L Gundlach1,2 & Andrew J Lawrence1,2. 1 The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria 3052, Australia. 2 Florey Department of Neuroscience and Mental Health, The University of Melbourne, Victoria 3010, Australia. Alcohol use disorders are a leading cause of preventable deaths worldwide and stress is a major cause of relapse. The relaxin-3/RXFP3 system modulates stress-induced relapse to alcohol seeking in rats and while the bed nucleus of the stria terminalis has been implicated in this regard, the central nucleus of the amygdala (CeA) also receives a relaxin-3 innervation and CeA neurons densely express RXFP3 mRNA. Moreover, the CeA is consistently implicated in both stress and addictive disorders. Yohimbine precipitates relapse-like behaviour in rodents, although exactly how yohimbine induces relapse is unknown, possibly by increasing stress levels and inducing a heightened cue reactivity. Since alcohol use causes neuroadaptations in brain stress circuits, in the current study, we examined the effects of yohimbine (1 mg/kg, i.p.) on anxiety-like behaviour in alcohol-experienced rats. Further, we assessed CeA neuronal activation following yohimbine-induced reinstatement of alcohol seeking, and the role of the relaxin-3/RXFP3 signalling within the CeA in yohimbine-induced reinstatement to alcohol seeking. Low dose yohimbine was anxiogenic in rats with a history of alcohol use. Furthermore, home-cage yohimbine treatment and yohimbine-induced reinstatement of alcohol seeking both increased Fos activation in CeA GABAergic neurons compared to naïve and vehicle controls. Bilateral intra-CeA injections of the selective RXFP3 antagonist, R3(B1-22)R, attenuated yohimbine-induced reinstatement of alcohol seeking. Collectively, these data suggest the CeA is a node where yohimbine acts to induce reinstatement of alcohol seeking and implicates the relaxin-3/RXFP3 system within the CeA in this process.

Galanin-3 receptor antagonism by SNAP 37889 blocks cue-induced reinstatement of alcohol seeking in IP rats and increases c-Fos expression in the nucleus accumbens shell. Kira-Elise Wilson1, Sigrid Limburg1, Melissa Duggan1, Adam J. Lawther1, Spencer J. Williams2, Andrew J. Lawrence3, Matthew W. Hale1†, Elvan Djouma4†. 1School of Psychology and Public Health, La Trobe University, Melbourne, Australia, 3086; 2Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Australia; 3Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia; 4School of Life Sciences, La Trobe University, Melbourne, Australia, 3086. Worldwide, 3.3 million people die each year due to the harmful use of alcohol, and 5.1% of the global burden of disease and injury is attributable to alcohol. The galanin-3 receptor subtype (GALR3) has been implicated in modulating the consumption of alcohol. We have previously shown that administration of the GALR3 antagonist SNAP 37889 decreases ethanol consumption in a fixed-ratio operant-responding paradigm, and attenuates cue-induced reinstatement. The current study employed an operant reinstatement paradigm to investigate the effects of SNAP 37889 on cue-induced reinstatement and c-Fos expression in the brains of alcohol-preferring (iP) rats. Eighteen iP rats were trained to self-administer 10% ethanol via a lever press, in the presence of visual and olfactory response-contingent cues. After 27 days of normal responding, response-contingent cues were then removed, leading to the extinction of lever-pressing behaviour. On the test day, rats were either treated with SNAP 37889 (30 mg/kg, i.p.) or vehicle (1ml/kg), before being exposed to operant chamber with the reinstatement of the visual and olfactory cues. Administration of SNAP 37889 reduced cue-induced reinstatement of ethanol-seeking behaviour. To examine the effect of GALR3

antagonism and cue-induced reinstatement on neuronal activation, c-Fos expression was measured in subregions of the medial prefrontal cortex (mPFC) and nucleus accumbens. Administration of SNAP 37889 increased c-Fos immunoreactivity in the nucleus accumbens shell, but was without effect in the nucleus accumbens core region or the prelimbic and infralimbic regions of the mPFC. Additionally, the colocalisation of c-Fos protein expression within putative dopaminergic neurons in the caudal ventral tegmental area (VTA) was studied using c-Fos/tyrosine hydroxylase dual-label immunohistochemistry. An independent-samples t-test revealed no differences in c-Fos expression in dopaminergic and non-dopaminergic cells in the caudal VTA, between SNAP 37889 and vehicle-treated rats. Results from the current study support previous findings of GALR3 involvement in cue-induced reinstatement of alcohol-seeking behaviour, and provide novel evidence that GALR3 antagonism induces heightened neuronal activity in the nucleus accumbens shell. These data further highlight the potential therapeutic utility of GALR3 antagonism for preventing relapse in alcoholism.

A novel automated home-cage task to assess motor skill learning and fine motor control in a mouse model of Huntington's Disease. Cameron L. Woodard1,2, Federico Bolaños1,2, James D. Boyd2, Timothy H. Murphy2, Lynn A. Raymond2. 1 Graduate Program in Neuroscience; 2 Department of Psychiatry and Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver BC Canada. Behavioral testing is a critical step in assessing the validity of rodent models of neurodegenerative disease, as well as evaluating the efficacy of pharmacological interventions. Recently, a number of automated systems have been developed to perform tracking and behavioral profiling of animals within their own home-cage, allowing for 24-hour monitoring and minimizing experimenter interaction. However as of yet, none of these systems have had functionality for the assessment of motor skill learning and fine motor control, which are highly relevant behaviours for movement disorders such as Huntington's and Parkinson's disease. To address this, we have adapted a novel paradigm that incorporates a lever-pulling task for water into the mouse home-cage. An automated system allows for continuous data collection over long periods (several weeks), and group-housed mice can be individually assessed via RFID tagging. Animals first learn a simple version of the task, before being moved to a second phase where they must hold the lever in a specified range of motion. Testing with this paradigm has revealed the presence of several distinct phenotypes in the YAC128 mouse model of Huntington's disease at 2 months (pre-symptomatic), 4-months (early symptomatic) and 6-months (symptomatic) of age. Pre-symptomatic, but not older, YAC128 mice display a decreased ability to adapt to changes in task demands when shifting to a more difficult task. In contrast, 4- and 6-month-old YAC128 mice exhibited circadian abnormalities and alterations on several kinematic measures, suggesting an impairment in motor control and persistence. As this system incorporates automated monitoring and minimal investigator interaction, we believe it has strong potential as a tool for the high-throughput identification of behavioral phenotypes in disease models. Support: Canadian Institutes of Health Research.

Sex differences and modulation by sex hormones of risk-based decision making with acute administration of amphetamine. Shunya Yagi1, Steven R. Wainwright1, Stephanie E. Lieblich2, Stan B. Floresco2, Liisa A. M. Galea1,2,3. Graduate Program in Neuroscience1, Department of Psychology2, Centre for Brain Health3, University of British Columbia.Vancouver Canada. Dopaminergic neurotransmission within the mesocorticolimbic pathway is known to alter risk-based decision making in rodents. Testosterone and estradiol levels have been shown to modulate reward related neural function and risk-taking behaviours in both men and women respectively and the gonadal hormones are known to

modulate dopaminergic tone and axon density within the nucleus accumbens and medial prefrontal cortex. The objectives of this study were to determine the effect of estradiol and testosterone on rodent performance within a probabilistic discounting task. Male and female Long-Evans rats were either bilaterally gonadectomized (GDX) or received sham-operation (Sham) All rats received single injections of vehicle, testosterone proprionate (0.2mg;1mg) or estradiol benzoate (0.3µg). After completion of hormone treatments we assessed the effects of amphetamine (0.125mg/kg;0.5mg/kg) on risk-based decision making. Rats were tested in a probabilistic discounting task in the operant chamber consisting of two levers; one the Large/Risky lever, the other the Small/Certain lever. Rats received daily sessions 6-7 days per week, consisting of 4 blocks of 18 trials that were comprised of 8 forced-choice trials where only one lever was presented (4 trials for each lever, randomized in pairs) permitting animals to learn the amount of food associated with each lever press and the respective probability of receiving reinforcement over each block. This was followed by 10 free-choice trials, where both levers were presented and the animal chose either the Small/Certain or the Large/Risky lever. Choice of the Small/Certain lever always delivered one pellet with 100% probability; choice of the Large/Risky lever delivered 4 pellets but with a particular probability. The probability of obtaining 4 pellets after pressing the Large/Risky lever was initially 100%, then 50%, 25%, and 12.5%, respectively, for each successive block. Our results demonstrate that males showed significantly greater choice of the large/risky lever in both the 25% and 12.5% probability trial blocks compared to females. High, but not low, testosterone treatment reduced risky decision making in the 12.5% probability trial blocks in the castrated rats, while estradiol treatment did not influence risky decision making either in males or females. Furthermore, the high dose of amphetamine increased lever pressing in the 25% probability trial blocks in the Sham group, and in the 12.5% probability trial blocks in both the Sham and GDX groups in regardless of sex. These findings indicate that testosterone modulates male risk related behaviors and gonadal hormones facilitate the effects of amphetamine to increase risky decision making. NSERC grant 203596-13.

Age-related neuroinflammatory responses associated with changes in learning impairments in a mouse model of Alzheimer's disease. Shenghua Zhu1,2, Jun-Feng Wang1,2, Xin-Min Li3. 1Department of Pharmacology and Therapeutics, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, 2 Kleysen Institute for Advanced Medicine, Health Sciences Centre, Winnipeg, MB, Canada, 3 Department of Psychiatry, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada. In Alzheimer's disease (AD), both amyloid deposition and neuroinflammation appear in the early course and become notably conspicuous as disease progresses. However, the progression of neuroinflammation and its relationship with amyloid deposition and behavioural changes have not been characterized as many underlying mechanisms rarely occur in isolation. Methods: The present study will thoroughly characterize the behaviour of the APP/PS1 mouse model of AD, using a comprehensive test battery designed to assess a variety of behaviours. Using a cross-sectional design, these behaviours will be assessed in mice at different ages. Brain pathology measures for amyloid deposition and neuroinflammation are done post-mortem. Results: APP/PS1 mice exhibited significant learning deficits from the age of 5 month, which were aggravated at the later stages of life. However, the degree of memory impairment plateaus after 12 months. Histological analyses showed that an early appearance of amyloid plaques at 3 months of age with a linear progressive increase up to 22 months. This pronounced amyloid deposition was accompanied by a steady increase of the glial fibrillary acidic protein (GFAP) positive astrocytes and CD11b positive microglia up to the age of 9-12 months. Interestingly the expression levels of GFAP rose steeply from the age of 5 months to the age of 9 months

and then stabilized at the age of 12 months which coincided with the observed pattern of learning deficits in APP/PS1 mice. Conclusions: These findings provided evidence that neuroinflammation might be involved in the development and progression of cognitive deficits in APP/PS1 mice, suggesting novel intervention and prevention strategies for AD.

WEDNESDAY, June 28

Keynote Speaker

08:00-09:00 **Using the Neurobiology of Will Power to Treat Drug Addiction.** Kalivas, Peter W. *Setouchi Hall, Room 1-2*

Using the Neurobiology of Will Power to Treat Drug Addiction. Kalivas, Peter W. The idea that psychiatric disorders, in particular drug addiction, arise from a problem of poor will power has been appropriately rejected in favor of biological hypotheses of disease etiology that can be used to develop rational behavioral and pharmacological treatments. However, by considering will power as a function of fidelity in the corticostriatal synapses mediating top-down regulation of behavior, we explore poor will power as an endophenotype of chronic drug use. We examine how enduring drug-induced changes in corticostriatal circuitry result in drug-associated cues becoming prepotent in guiding behavior, such that an addict chooses to seek drug over engaging more adaptive behaviors. While some understanding of the drug-induced adaptations has developed from studying classic pre- and postsynaptic physiology, it has been necessary to study all aspects of tetrapartite synaptic plasticity (pre- and postsynapse, astroglia and extracellular matrix) in prefrontal cortical synapses in the nucleus accumbens to gain a more accurate and complete understanding of how addictive drugs create vulnerability to relapse. Following self-administration, enduring adaptations are produced in astroglial regulation of glutamate transmission. These enduring adaptation result in reinstated drug-seeking induced by conditioned cues becoming associated with transient synaptic potentiation in accumbens medium spiny neurons that is required for reinstatement. Transient synaptic potentiation requires signaling through neuronal nitric oxide synthase interneurons that, in turn, activates the extracellular matrix. After outlining the enduring changes and transient sequence of events in prefrontal-accumbens tetrapartite synapses, we will discuss how pharmacological reversal of these adaptations prevents cued drug-seeking in the reinstatement model of relapse. Moreover, these biologically-based strategies have led to clinical trials with one compound, N-acetylcysteine, that successfully inhibits the intrusive motivation leading to inappropriate drug seeking. However, the trials also show that reduced intrusive thinking (craving) does not always decrease rates of relapse, indicating that the compound will likely be useful only for a subpopulation where intrusive drug craving is a critical trigger for relapse.

09:30-11:30 **Symposium: Advances in Behavioral Neuroscience in Japan and Diversity of DAergic Regulation.** Chairs: Yoichi Ueta and Kiyofumi Yamada. *Setouchi Hall, Room 6*

Memory enhancement by food intake involves epigenetic modulation of BDNF and acidic FGF genes expression. Yutaka Oomura, Toshihiko Katafuchi. Department of Integrative Physiology Faculty of Medicine, Kyushu University, Fukuoka, Japan. We have previously reported that, an intra-hippocampal injection of 7 mM glucose, which is similar to the glucose concentration of the cerebrospinal fluid during food intake, facilitates spatial learning and memory in rats. In the present study, we show that the glucose-induced enhancement of spatial memory is due to an increment of BDNF, which is possibly caused by: (1) Increase in recruitment of p-CREB onto the brain derived neurotrophic factor (BDNF) and fibroblast

growth factor-1 (FGF-1) promoters, CREB is activated by glucose-induced p-AKT. (2) Decrease in histon deacetylase (HDAC) recruitment and increased acetylation near the BDNF andFGF-1 promoters. To clarify the above we used cultured neurons, NA2 cells. Conclusion: 1) When glucose was increased from 3.5 to 7 mM, N2A cells showed an increase in the expression of BDNF and FGF-1 along with the enhanced phosphorylation of AKT (PKB) and CREB. 2) The glucose-induced up-regulation of BDNF was blocked by the knock down of CREB using lenti-viruses encoding short hairpin-RNA against CREB. 3) The high glucose increased CREB recruitment onto the BDNF and FGF-1 promoters. 4) The glucose stimulation reduced HDAC recruitment and increase acetylation near the BDNF and FGF-1 expression in mice. 6) Glucose drinking increased number of dendritic spines and tetanus-induced LTP in mouse hippocampus. 7) Glucose drinking increased activated p-Akt and CREAB, as well as acetylated histons in the hippocampal tissues. 8) Knock down of hippocampal TrkB blocks glucose-induced enhancement of spatial memory in mice.

Behavioral study based on hippocampal theta power. Shogo Sakata1 & Yuya Sakimoto2. 1Hiroshima University, 2Yamaguchi University, Japan. The hippocampus plays a very important role in animal behavior, particularly with respect to memory, the navigation system, place recognition, and learning. The hippocampus is critically involved in many kinds of stimulus discrimination tasks. This talk will focus on learning behavior, especially the narrow range of operant stimulus discrimination learning in rats. Many in vitro studies have been carried out in the field of neuroscience, but more high-quality in vivo research is needed in the field of behavioral neurosciences, especially in relation to leaning behavior. Using the measure of electrical activity in the animal's brain, we can observe interesting activity patterns. The most prominent hippocampal encephalography (EEG) frequency recorded from the hippocampal formation is composed of theta waves. In the rat, hippocampal theta waves consist of rhythmic, often sinusoidal oscillations that vary in frequency from 6 to 12 Hz called hippocampal theta. I will present important hippocampal EEG findings in connection with several stimulus discrimination learning. A number of studies have suggested that hippocampal theta activity is related to learning and movement. We have indicated that an increase in hippocampal theta power occurs during a negative patterning (NP) task after presented the compound stimulus (AB-). Also our studies have indicated that a short decline in hippocampal theta power occurs during response inhibition under a conflict state in a go/no-go stimulus discrimination task. To induce a conflict state, an NP task, a feature negative (FN) task and a positive patterning (PP) task were used in some previous studies. For an example of the NP task, rats were trained to carry out a lever press response upon the presentation of each element stimulus A+, B+ and in contrast, to withhold a lever press response upon presentation of stimulus AB-. As a result, a conflict state leading to response inhibition was induced in the case of the compound stimulus (AB-), as it elicited a go and no-go response tendency. We examined the relationship between hippocampal theta activity and response inhibition and discovered that hippocampal theta power declined transiently during response inhibition to a compound stimulus in NP and FN tasks, but not for non-reinforced stimuli in a simple discrimination (SD) task. Thus, we hypothesized that the transient decline in hippocampal theta power is induced by behavioral inhibition for stimuli that have an overlapping element. I will explain how this hippocampal theta activity sheds interesting light upon stimulus discrimination and temporal discrimination learning.

Life-long hormonal and experiential influences on social brain. Sonoko Ogawa1, Kazuhiro Sano2, Shinji Tsukahara3. 1Laboratory of Behavioral Neuroendocrinology, University of Tsukuba, 2 Department of Pharmacology, Aichi Medical University, 3 Graduate School of Science and Engineering, Saitama University. To understand neural basis of social behavior, it is essential to study the life-long action of hormones as well as environmental and experiential influences on the brain. It is well known that gonadal

steroid hormones, androgen and estrogen, regulate the expression of sex-typical sexual and aggressive behavior through organizational and activational action. Studies using knockout mouse models revealed that not only estradiol but also testosterone after being aromatized to estradiol in the brain acts through estrogen receptor (ER) α and/or β to regulate sexual and aggressive behavior in both sexes. To investigate possible neural basis of these behavioral changes, we performed neuroanatomical analysis for sexually dimorphic brain areas, such as the principal nucleus of bed nucleus of the stria terminalis (pBNST) and anteroventral periventricular nucleus (AVPV) using knockout mice for aromatase, ERα, and ERβ. These studies have revealed that both masculinization of male-dominant (male > female) pBNST and defeminization of female-dominant (female > male) AVPV require ERα, but not ERβ, mediated action of estradiol in male mice. Furthermore, in our behavioral studies with the use of virally mediated RNAi method, we found that ER activation in the medial amygdala during pubertal period, but not at the time of testing in adult, is crucial for male mice to fully express male-type sexual and aggressive behaviors in adulthood. In this study, it was also found that number of neurons in this brain area examined in adult was reduced by pre-pubertal knockdown of ER. On the other hand, ER activation in the medial preoptic area for sexual behavior and in the hypothalamic ventromedial nucleus for both sexual and aggressive behaviors is necessary at the time of testing in adult. These findings collectively suggest time-, sex-, and brain site-specific action of gonadal steroid hormones in the regulation of brain function and behavior. In addition, detailed behavioral analysis focusing on social interactive behaviors including social preference, social recognition and social memory as well as emotional and anxiety-related behavior in social context revealed that this wide range of social behavior may be influenced by neonatal and pubertal social environment. In this talk, we will overview these behavioral neuroendocrine research and discuss possible future direction. (Supported by KAKENHI #15H05724 to SO).

Discovery of a novel reward signal in the striatum. Taku Nagai1, Keisuke Kuroda2, Kiyofumi Yamada1, Kozo Kaibuchi2. 1Department of Neuropsychopharmacology and Hospital Pharmacy, 2Department of Cell Pharmacology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. Dopamine signaling in the brain is a complex phenomenon that strongly contributes to emotional behaviors. The principal targets of dopamine are medium spiny neurons (MSNs), which are a special type of GABAergic inhibitory cell that represents 90% of the neurons in the striatum. There are distinct classes of spatially intermixed MSNs that express dopamine D1 (D1R-MSNs) or D2 receptors (D2R-MSNs). MSNs express a number of specific signaling proteins that differ markedly from those in other brain regions and that determine the characteristics of the cAMP/protein kinase A (PKA) signaling pathway. Dopamine-PKA signaling has numerous cellular targets, including glutamate receptors, voltage-dependent ion channels and transcription factors in the MSNs. To explore the novel downstream PKA signaling events in the MSNs, we developed kinase-oriented substrate screening (KiOSS) method as a novel proteomic approaches for more comprehensive screening. Using this approach, we comprehensively identified PKA substrates downstream of D1Rs in the striatum of mice, and found more than one hundred candidate substrates of PKA, including Rap1 GEF (Rasgrp2). Based on our findings, we propose the following mechanism for dopamine-dependent reward signaling in vivo. The binding of dopamine to D1Rs activates PKA to phosphorylate Rasgrp2. The phosphorylation of Rasgrp2 leads to Rap1 activation, followed by recruitment of the MAPK pathway, which increases the excitability of accumbal D1R-MSNs. The enhancement of D1R-MSN excitability increases spike firing in response to excitatory glutamatergic input from the cortex and/or thalamus. Subsequently, the axonal pathway of D1R-MSNs becomes more dominant than the D2R-MSN pathway, eventually resulting in the expression of reward-associated emotional behaviors (Nagai et al., Neuron, 2016; Trens Pharmacol Sci, 2016). We believe that

our phospho-proteomic screening is a powerful and useful tool to increase molecular-level understanding of multifarious brain functions by elucidating the function of the dopamine.

Coordinated expression of learned motor behavior through striatofugal pathways. 1Kobayashi, Kazuto; 1Iguchi, Yoshio; 1Nishizawa, Kayo. 1Fukushima Medical University. Dopamine neurons originating from the ventral midbrain have an important role in motor control and learning processes through the basal ganglia circuit. The dorsal striatum, a key structure of basal ganglia circuit, receives dopaminergic inputs from the susbtantia nigra pars compacta in addition to glutamatergic inputs from many cortical and thalamic regions, and mediates the processes contributing to instrumental learning. Striatofugal pathways are composed of two subpopulations of GABAergic medium-sized spiny neurons that constitute the direct and indirect pathways. These two striatofugal pathways are considered to regulate motor functions through their opposing influences on the output activity. However, the neural mechanism underlying these striatofugal pathways control the processes of instrumental learning has not been fully understood. Our research group addressed the roles of these two pathways in stimulus-response learning paradigms, in which animals learn to select appropriate responses dependent on different stimuli. Cell targeting approach indicated that the direct pathway from the dorsomedial striatum is involved in the response time modulation with no influence on the selection accuracy in visual discrimination and that the indirect pathway from the dorsolateral striatum mainly contributes to the control of the selection accuracy of learned motor responses in auditory discrimination. To more clearly understand the behavioral roles of these two pathways, it is important to evaluate the roles of the pathways with the same behavioral paradigm. We address the behavioral significance of striatal direct and indirect pathways from the dorsomedial striatum in the auditory discrimination task of transgenic rats by using cell targeting and chemical genetic approaches, suggesting the cooperativity of the two striatofugal pathways to regulate the selection accuracy and response time of learned motor actions in the performance of stimulus-response learning.

09:30-11:30 **Symposium: Neurobiological mechanisms of social and non-social reward.** Chairs: Alexa Veenema and Edward Nieh. *Setouchi Hall, Room 1-2*

Lateral Hypothalamic Control of Motivated Behaviors through the Midbrain Dopamine System. Edward H. Nieh1, Caitlin M. Vander Weele1, Gillian A. Matthews1, Kara N. Presbrey1, Romy Wichmann1, Christopher A. Leppla1, Ehsan M Izadmehr1, Kay M. Tye1. 1The Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology (MIT), Cambridge, MA 02139, USA. The lateral hypothalamus (LH) and ventral tegmental area (VTA) have been ascribed a variety of reward-related functions. LH projections to the VTA encode conditioned responses and control feeding behavior, and GABAergic neurons in the LH promote appetitive behaviors. Here, we show that the GABAergic component of the LH-VTA pathway supports positive reinforcement and place preference, while the glutamatergic component of the LH-VTA pathway mediates place avoidance. In addition, our results indicate that photoactivation of these projections promotes other behaviors, such as social interaction and perseverant investigation of a novel object. We demonstrate that photostimulation of the inhibitory GABAergic LH-VTA component, and not the excitatory glutamatergic component, increases dopamine (DA) release in the nucleus accumbens (NAc), which occurs via inhibition of local VTA GABAergic neurons. Our study clarifies how GABAergic LH inputs to the VTA can broadly regulate motivational salience by disinhibiting VTA dopamine inputs to the NAc.

Nucleus accumbens dopamine D1-receptor-expressing neurons control incentive salience to reward-predictive cues. Tom Macpherson1, Takatoshi Hikida1. 1Medical Innovation Center, Kyoto University Graduate school of Medicine, Kyoto, Japan. Considerable evidence has implicated the nucleus accumbens (NAc) in the control of motivated behaviours, including instrumental responses towards primary or conditioned reinforcers. Indeed, dysfunction of the NAc is known to contribute to a number of decision-making-associated neuropathologies, including addiction and schizophrenia. However, it is still unclear how attribution of motivational value (incentive salience) towards primary rewards, or environmental stimuli predictive of rewards, may be controlled by the activity of NAc striatonigral (direct) and striatopallidal (indirect) projection neurons. Here we explore the D1-expressing and D2-expressing neurons originating from three striatal subregions, the nucleus accumbens (NAc), the dorsomedial striatum (DMS), and the dorsolateral striatum (DLS), in mediating Pavlovian approach behaviour in an autoshaping task. Using a reversible neurotransmission blocking (RNB) technique (as described in Hikida et al, 2010) to separately inhibit activity in each neuron group, we revealed a specific role of NAc D1-expressing neurons in controlling Pavlovian approach behaviour to an environmental cue associated with a natural food reward. Blockade of NAc D1-expressing neuron activity impaired sign-tracking responses to the CS, while leaving goal-tracking responses intact. These findings provide insight into the neural circuits underlying Pavlovian conditioning, and may be important in the identification of therapeutic targets for the treatment of disorders associated with a loss of impulse control, including addiction. This study was supported by the MEXT/JSPS KAKENHI Grant Numbers 15F15107, 23120011 and 15H04275.

Neuronal correlates of motivational sensitivity to natural and drug rewards. B. O'Donovan1, R. Robke2, S. Saramanayake2, P. Hashemi2, P.I. Ortinski1. 1Department of Pharmacology, Physiology and Neuroscience, University of South Carolina School of Medicine. Columbia, SC; 2Department of Chemistry and Biochemistry, University of South Carolina. Columbia, SC. Individual differences in motivation for natural rewards may predict future response to psychostimulants. Regulation of motivated behavior is known to be dependent on dopamine signaling in the nucleus accumbens (NAc) shell. However, the neuronal mechanisms underlying motivation remain largely unexplored. This study evaluates the mechanisms underlying individual differences in motivation for natural reward, and the effect of motivational state on neuronal response to cocaine. Rats were identified as high (HighS) and low (LowS) motivated responders based on their performance on a sucrose self-administration task. Following the final behavioral session, dopamine levels in the NAc shell were measured using fast scan cyclic voltammetry (FSCV) and fast scan adsorption controlled voltammetry (FSCAV), or slices containing NAc were prepared and whole-cell patch clamp recordings were performed from NAc shell medium spiny neurons (MSNs). A separate group of HighS and LowS rats were exposed to cocaine self-administration prior to whole-cell patch clamp recording. HighS rats had elevated levels of phasic and tonic dopamine and slower dopamine clearance in the NAc shell when compared to LowS rats. NAc shell MSNs in LowS rats are significantly more excitable than MSNs in HighS rats. Differences in the action potential waveform, and further investigation in the MidS rats, indicate that the difference in excitability is mediated by differences in potassium channel activity. Cocaine exposure resulted in suppressed firing of NAc shell MSNs in the LowS, but not the HighS, group. Individual differences in motivation for a sucrose reward are linked to alterations in dopamine signaling in the NAc shell. The greater excitability of MSNs in LowS rats appears to be due to the lower level of dopamine signaling in this group. Differences in motivation are also associated with susceptibility to cocaine-induced intrinsic plasticity. We are now further exploring the mechanisms via which dopamine signals may modulate MSN excitability.

Role of opioid and vasopressin systems in socially rewarding behaviors. Alexa H. Veenema[1,2], Caroline J. Smith[2], Remco Bredewold[1,2]. [1]Department of Psychology, Michigan State University, East Lansing, MI, USA, [2]Department of Psychology, Boston College, Chestnut Hill, MA, USA. Juvenile animals seek out interactions with novel peers more frequently and find these interactions to be more rewarding than their adult counterparts. Here, we begin to explore the mechanisms mediating juvenile social reward by focusing on social novelty-seeking and social play behavior. We will discuss data showing that male and female juvenile rats spend more time interacting with a novel conspecific than a cage mate. We further find that this social novelty-seeking behavior is impaired upon social isolation but can be restored by activation of the mu-opioid receptor in the nucleus accumbens. We will also show that the vasopressin system modulates social play behavior in juvenile rats, but does so in sex-specific ways. We will provide evidence suggesting the involvement of glutamate in the lateral septum in the sex-specific regulation of social play by vasopressin. Unraveling the neuronal mechanisms underlying social novelty-seeking and social play behavior may be a first step toward understanding the neural basis of abnormalities in these socially rewarding behaviors as seen in children diagnosed with autism spectrum disorders. This research was supported by NSF GRFP 2012138127 to CJWS and NSF IOS1253386 and NIMH R01MH102456 to AHV

13:30-15:30 **Symposium: Assessing changes in cognitive and affective behavior in models of acute neurologic injury.** Chair: Farida Sohrabji. *Setouchi Hall, Room 6*

Assessing depression in a rodent model of spinal cord injury. M.A. Hook1,2, Brakel, K.1,2, Aceves, M.1,2. 1Texas A&M Health Science Center, Department of Neuroscience and Experimental Therapeutics, 2Texas A&M Institute for Neuroscience. In addition to decreased physical function, spinal cord injury (SCI) is associated with debilitating effects on psychological well-being, often manifest as depression and anxiety. In fact, the incidence of depression as well as the associated suicide risk, is estimated to be 3 or more times greater in the SCI population compared with the general population. At present, however, clinical strategies aimed at treating depression are limited, and depression remains refractory for many patients. The success of therapies is likely impeded by a limited understanding of the molecular changes underlying subtypes of depression. To address this, we have developed a novel strategy for behaviorally phenotyping rats as depressed or not-depressed following SCI. Rats are given a moderate spinal contusion injury and then tested on a battery of tasks, thought to measure symptoms analogous to those observed in the clinical population, on days 1-2, 9-10, and 19-21 post-injury. Using hierarchical cluster analyses to characterize the subjects based on a constellation of symptoms, an approach akin to clinical diagnoses, we have found that approximately 30% of SCI rats exhibit depression-like behaviors. These subjects display decreased sucrose preference, open field activity, social exploration, and increased immobility on the forced swim test. Notably, however, many of these tests rely on motor activity, and in the SCI model performing these behaviors may be compromised by the motor impairments inherent to the injury. We have tested the impact of motor-impairment on the characterization of depression in several ways. First, we compared locomotor recovery levels and post-mortem lesion size between depressed and not-depressed SCI subjects. Both groups displayed comparable levels of recovery and spinal lesion size. Second, using implantable telemetry devices, we have shown that relative to intact and not-depressed SCI subjects, SCI subjects characterized as depressed have significantly higher heart rates and decreased heart rate variability. Interestingly, higher heart rates and decreased heart rate variability are also associated with depression in humans. At a molecular level, the rats characterized as depressed also have higher pro-inflammatory cytokine expression in the serum than not-depressed rats. The elevation of serum levels of pro-inflammatory cytokines in the depressed subset of subjects is also reminiscent of that

seen in patients with depression disorders. For this SCI model, therefore, non-subjective measures that are not contingent on motor performance support the behavioral characterization of depression. With this unique animal model we aim to systematically identify critical molecular changes that underlie the development of depression-like symptoms after SCI. Research support: Gilson-Longenbaugh Foundation and Mission Connect, a project of the TIRR foundation.

Behavioral correlates of TBI neuropathology; underlying mechanisms of escalated alcohol drinking. Jacques Mayeux1, Zack Stiepler1, Nicholas Gilpin1, Jason Middleton2, Scott Edwards1, Patricia Molina2. 1Department of Physiology, Alcohol and Drug Abuse Center of Excellence, Louisiana State University Health Sciences Center, New Orleans, LA, 70112. 2Department of Cell Biology and Anatomy, Alcohol and Drug Abuse Center of Excellence, Louisiana State University Health Sciences Center, New Orleans, Louisiana. Traumatic brain injury (TBI) is characterized by an early and sharp rise in neuroinflammation followed by a protracted secondary wave of sustained neuroinflammation that is associated with lasting neurological and behavioral deficits that include increased incidence of anxiety and depression, stress and pain sensitivity, as well as anhedonia and impulse control deficits. These TBI sequelae promote alcohol abuse in humans through unknown mechanisms. Alcohol exposure post-TBI augments and sustains neuroinflammation and excitatory glutamate signaling, and impairs neurobehavioral recovery from TBI. Our aim is to understand the underlying mechanisms leading to escalation in alcohol drinking post-TBI. Modulation of endocannabinoid (EC) tone by systemic administration of JZL184, a monoacylglycerol lipase (MAGL) inhibitor that prevents degradation of the endocannabinoid (EC) 2-AG is sufficient to attenuate neuroinflammation and improve neurobehavioral recovery. We tested the hypothesis that post-TBI EC degradation inhibition would improve neurobehavioral outcomes including escalation of alcohol drinking. Adult male Wistar rats were trained over four weeks to self-administer alcohol in a 30-minute, free choice two lever FR1 operant paradigm with one press of one lever delivering 0.1 ml water and one press of the other lever delivering 0.1 ml 10% w/v alcohol. Following stabilization of voluntary drinking, rats were counterbalanced into: sham, TBI+VEH, and TBI+JZL. All rats underwent a 5-mm left lateral craniotomy, and TBI was induced by lateral fluid percussion. Thirty minutes post-TBI, rats received i.p. injections of JZL184 (16 mg/kg) or vehicle. Rats were allowed to self-administer alcohol for two weeks post-TBI before sacrifice and brain collection for biochemical analysis. Anxiety-like behavior (open field test), cognitive deficits (Y-maze), pain sensitivity (Von Frey test), and motivated alcohol drinking (progressive ratio operant self-administration; PR) were assessed up to two weeks post-TBI. Our results show that a single injection of JZL184 post-TBI decreases motivation to drink (PR), attenuates neuroinflammation, rescues dysregulated glutamatergic signaling, and attenuates neuronal hyperexcitability at the site of injury. JZL184 administered-TBI animals had significantly improved cognitive performance, significantly attenuated pain sensitivity deficits, and significantly attenuated anxiety-like behavior compared to vehicle-injected TBI animals. These results show that modulation of EC tone post-TBI has potential therapeutic benefits that persist throughout the acute recovery period (14 days post-TBI). We speculate that TBI-induced synaptic hyperexcitability at the site of injury may contribute to the development of negative affective behaviors including anxiety-like behavior and escalation of alcohol self-administration post-TBI. Research Support: NIAAA T32AA007577, DOD W81XWH-11-2-0011, LEQSF-EPS (2012)-PFUND-283.

Evaluation of social cognition in neural injury. Choleris, Elena1; Phan, Anna1; Matta, Richard1; Ervin, Kelsy S.1; Kavaliers, Martin1,2. 1Department of Psychology and Neuroscience Program, University of Guelph, Guelph, ON, Canada. 2Department of Psychology, University of Western Ontario, London, ON,

Canada. The consequences of brain injury are often investigated in rodent models. However, the long-term effects on psychosocial and cognitive behavior are often understudied, possibly because of the challenge of studying learning and memory in animals that may have partly impaired motor functions or other insults, including enhanced stress and immune responses. We present here a few behavioral tests that require only limited training and locomotion and as such we believe can be used or modified for male and female rodents with brain injury. Social recognition, the discrimination of members of a social group, is an established social cognitive skill that does not involve extensive locomotion. Other social tests give choices between a social and a non-social stimulus (so-called sociability test) or social stimuli of difference salience (e.g. between individuals of differing sexual attractiveness in mate choice situations). Similarly, the adaptive acquisition of information from others via social learning, often investigated with the social transmission of food preferences, can be assessed also with limited locomotion/activity. In all tests, the discrimination between social cognitive effects from hypolocomotion can be achieved with comprehensive behavioral assessments of social interactions. When effects of brain injury are found in these tests, additional investigations can be performed to determine whether or not the effects are specific to "social" cognition, generalize to other cognitive skills, or are secondary to sensory impairment. For example, when social recognition is affected, further investigations can assess recognition of objects or spatial locations. Similarly, when impairments in the social transmission of food preferences, are found, olfactory/sensory discrimination of the flavored foods used in the test needs to be determined. In this specific case, we provide an example of how judicious modifications of the testing conditions have allowed the investigation of olfactory discrimination in hypoactive mice. Lastly, we show how specific modifications of the tests for social recognition and social learning enable the assessment of either impairing or enhancing effects of experimental manipulations. Specifically, by modifying the learning sessions we developed "easy" and "difficult" versions of the tasks. The difficult versions where control groups cannot perform the task, allow for the assessment of enhancing effects of treatment, whereas the easy versions, with good learning in control animals, enable the investigation of impairing effects. Together, the array of tests presented here can allow the assessment of the effects of brain injury on specific or generalized social cognitive skills. Supported by NSERC.

Targeting effort-related motivational dysfunction in neurological and psychiatric disorders: Animal models. John D. Salamone1, Merce Correa1,2, Jen-Hau Yang1, Renee Rotolo1, Rose Presby1, Samantha E. Yohn1. 1Department of Psychological Sciences, University of Connecticut, Storrs, CT, USA 06269-1020. 2Department of Psicobiology, Universitat Jaume I, 12071 Castelló, Spain. Motivational symptoms such as anergia, fatigue, or apathy are frequently observed in patients with depression, schizophrenia, Parkinsonism and other disorders. Depressed people show reduced selection of high-effort alternatives, and tasks that measure effort-based choice are being developed as animal models of motivational symptoms. In rodents, effort-based choice tasks allow animals to select between a more valued reinforcer that can only be obtained by a high degree of effort versus a low effort/low reward option. Low doses of dopamine (DA) antagonists and accumbens DA depletions shift choice behavior, decreasing selection of the high effort option and increasing choice of the low effort option. Alterations in effort-based choice in rodents are induced by conditions associated with depression, such as injection of tetrabenazine (TBZ), which blocks monoamine storage, and by pro-inflammatory cytokines (IL-1 and IL-6). The drug-induced deficits in effort-based choice can be used to assess the effects of known and potential therapeutic agents. Several drugs have been shown to reverse the effort-related effects of TBZ or cytokines, including the DA uptake blockers bupropion, GBR12909, methylphenidate, modafinil, PRX-14040, and lisdexamfetamine (LDX). The norepinephrine (NE) uptake blocker desipramine does not reverse the effects of TBZ, nor do

the serotonin uptake blockers (SSRIs) fluoxetine or S-citalopram. The lack of effect of SSRIs is consistent with clinical reports showing that SSRIs are relatively ineffective for treating fatigue and anergia, and can exacerbate these symptoms. We also assessed the ability of drugs to increase work output in rats tested on a progressive ratio (PROG)/chow feeding choice task. Acute and repeated injections of bupropion, GBR12909, LDX and PRX-14040 increased PROG work output. In contrast, fluoxetine, desipramine, and the NE uptake blocker atomoxetine failed to increase lever pressing output, and actually decreased it at higher doses. Bupropion and GBR12909 at behaviorally active doses elevated extracellular DA in accumbens as measured by microdialysis, while fluoxetine, desipramine and atomoxetine did not. Mouse paradigms for characterizing genetic factors that contribute to effort-related choice also have been developed. These results demonstrate that effort-related motivational symptoms can be modeled in rodents, and suggest a role for DA in regulating these symptoms.

13:30-15:30 **Symposium: Insights from studying contrasting circuits and mechanisms underlying adaptive coping.** Chair: Jason Radley. *Setouchi Hall, Room 1-2*

Circuits for the organisation and modulation of defensive behaviour in the rat. Gavan P. McNally[1], [1]University of New South Wales, Sydney, Australia. Foraging animals balance the need to seek food and energy against the accompanying dangers of injury and predation. To do so, they rely on learning systems encoding reward and danger. Whereas much is known about these separate learning systems, little is known about how they interact to shape and guide behavior. Here we show a key role for the rat paraventricular nucleus of the thalamus (PVT), a nucleus of the dorsal midline thalamus, in this interaction. First, we show behavioral competition between reward and danger: the opportunity to seek food reward negatively modulates expression of species-typical defensive behavior. Then, using a chemogenetic approach expressing the inhibitory hM4Di designer receptor exclusively activated by a designer drug in PVT neurons, we show that the PVT is central to this behavioral competition. Chemogenetic PVT silencing biases behavior toward either defense or reward depending on the experimental conditions, but does not consistently favor expression of one over the other. This bias could not be attributed to changes in fear memory retrieval, learned safety, or memory interference. Rather, our results demonstrate that the PVT is essential for balancing conflicting behavioral tendencies toward danger and reward, enabling adaptive responding under this basic selection pressure. Supported by the Australian Research Council and National Health and Medical Research Council.

A basal forebrain interface for coordinating endocrine and behavioral responses to stress. Jason J. Radley, Ph.D., Dept. of Psychological and Brain Sciences and Neuroscience Program, University of Iowa, Iowa City, IA, USA. Responses to stress involve the recruitment of neural circuits to modify behavioral and neuroendocrine systems that promote adaptive coping. Dysfunction of stress modulatory CNS pathways has been widely implicated in a variety of neuropsychiatric diseases, yet these mechanisms remain poorly understood. Here we present recent data from our laboratory that implicates the anteroventral subdivision of bed nuclei of the stria terminalis (avBST) as a neural hub for inhibiting both HPA activation and passive behavioral responses to inescapable challenges in rats. Follow-up studies will highlight evidence that avBST receives and relays influences from upstream cortical regions, most notably the medial prefrontal cortex, in promoting these adaptive responses. Finally, we will consider how perturbations in this modulatory circuit may lead to chronic stress-related dysfunction of multiple systems.

Stress hypothalamic-pituitary-adrenal (HPA) axis habituation is met by differential changes in the serotonergic system of male and female rats. Victor Viau. The University of British Columbia, Vancouver, Canada V6T 1Z3. Governed by the hypothalamic-pituitary-adrenal (HPA) neuroendocrine axis, stress-induced elevations in circulating glucocorticoids are adaptive in that they allow the organism to meet the energetic demands of threats to the body. However, chronic or sustained elevations in glucocorticoids are maladaptive and are often associated with mood, metabolic, and cardiovascular disorders. Despite marked sex disparities in the prevalence of these disorders, few studies have explored sex differences in stress HPA axis habituation, defined as a reduction in glucocorticoid responsiveness when exposed to the same stimulus in a predictable manner. Data will be presented to underscore that during repeated restraint exposure males and females show comparable declines in HPA output, as well as similar habituation of cellular activation (Fos) responses in the brain, indicating common CNS substrates of stress adaptation in males and females. We have additional evidence, however, to suggest that the process of stress habituation involves a reduction in serotonin (5-HT) stimulatory control over the HPA axis, resulting from changes in 5-HT synthesis and receptor gating that are unique to each sex. Within the raphe nucleus, the principle source of 5-HT in the brain, only females showed a reduction in 5-HT synthesis after repeated restraint. However, only males showed increased expression of the presynaptic 5-HT 1A receptor, which normally diminishes excitability of 5-HT raphe neurons. Both mechanisms to reduce 5-HT transmission may well serve habituated responses in males and females, but may also be relevant to sex differences in mood disorders. This study was supported by the Canadian Institutes of Health Research (VV).

Prefrontal glucocorticoid signaling mechanisms and stress integration. James P. Herman1, Jessica M. McKlveen1, Yueh-Chiang Hu2, Parinaz Mahbod1, Rachel Morano1, Jessie Scheimann1 and Rachel Moloney1. 1Dept. of Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH 45237, and 2Div. of Developmental Biology, Cincinnati Children's Medical Center, Cincinnati, OH, 45267. Multi-component circuits are critical for control of physiology and behavior, both in the context of adaptation and pathology. Neuroanatomical and functional studies have defined tripartite regulation of stress reactivity, involving prefrontal and hippocampal inputs that limit stress responses and amygdala inputs that appear excitatory. Importantly, all three of these structures express an abundance of glucocorticoid receptors (GRs), which integrate stress hormone signals into appropriate changes in network reactivity. To query the role of the prefrontal cortical GR in stress homeostasis, we have used viral vector-based technologies to drive GR knockdown in the infralimbic cortex (IL). In rats, shRNA-mediated knockdown of GR in the IL (but not prelimbic) cortex causes enhanced HPA axis responsiveness to both acute and chronic stress, and enhanced immobility in the forced swim test, suggesting a role for the IL GR in limiting behavioral and physiological stress reactivity. In addition, chronic stress causes a marked enhancement of inhibitory synaptic drive in the IL, consistent with a loss of function. Enhanced inhibition is associated with marked reductions in number of GR immunoreactive GABAergic interneurons, suggesting a selective impact of stress on this cell population. Current studies are using rat model of conditional GR deletion (generated using CRSIPR/Cas9 methods) to test cell type and circuit mechanisms mediating prefrontal stress control.

16:00-18:00 **Symposium: Species-specific signals for protection of the social group.** Chairs: Markus Fendt and Yasushi Kiyokawa. *Setouchi Hall, Room 6*

To call or not to call: Assessing the determinants of vocalizing by isolated guinea pig pups. Michael B. Hennessy1, Patricia A. Schiml1, Terrence Deak2. 1Wright State University, 2Binghamton University. The calling of young separated from their mother is ubiquitous among mammals. Yet the function of these

calls and the context in which they are emitted vary greatly among species. Helpless, newborn rat (Rattus novegicus) and mouse (Mus musculus) pups emit ultrasonic signals to elicit retrieval to the nest. In contrast, for the domestic guinea pig (Cavia porcellus) and its wild progenitor species (Cavia aperea), pups are well-developed at birth; mothers do not retrieve pups; and there is no nest. Moreover, C aperea serves as prey for a variety of avian, mammalian, and reptilian species. Whether pups vocalize during separation depends greatly on context. C. porcellus pups placed alone in a brightly lit and open novel environment vocalize at a high rate and exhibit activation of the hypothalamic-pituitary-adrenal axis. However, these responses are minimal or non-existent if pups are left alone in the home cage, or isolated in a darkened, enclosed novel environment. Further, the vocalizing of isolated pups is time-limited. After an hour or so, pups quiet, assume a hunched posture and become immobile. This second stage resembles the behavior of physically ill animals and can be reduced with anti-inflammatory treatment. Together these results suggest that the context and temporal pattern of vocalizing by guinea pig pups reflects a balance between the need to re-establish maternal contact and the need to avoid attracting predators, and that neuroimmune signaling molecules mediate the transition from active/vocalizing to the quiet/immobile stages of separation.

Emission of rat vocalizations as the mechanism of ethotransmission. Stefan M. Brudzynski, Brock University, St. Catharines, Ontario, Canada. The term ethotransmission was introduced for the first time in 2010 and was based on extensive studies of rat ultrasonic vocalizations and the brain systems that initiate these vocalizations. The ethotransmission is understood as a social transmission of emotional arousal by species-specific signals from the sender to the receiver. The signals initiate emotional state in the receiving animal in a direct way, i.e., without other environmental inputs. Ultrasonic vocalizations are emitted by rats as a result of emotional arousal and emotional state of the signaler, thus, ethotransmission represents a direct emotional communication conveyed by specific vocal signals in such a way that emotional state of the signaling animal is transferred to the animal(s) receiving the signal. In other words, emotional state of the vocalizer causes direct initiation of the equivalent emotional state in the listener using specific communicatory signals. This is a specific form of communicatory transfer of emotional state, since other non-specific environmental alarming of arousing stimuli do not represent ethotransmission. Ethotransmission may be compared to neurotransmission at the level of individual neurons, where not any depolarizing agent is a neurotransmitter. Rats are emitting two fundamental groups of species-specific ultrasonic vocalizations labeled 22 kHz calls and 50 kHz calls. The 22 kHz vocalizations are initiated by the activity of the ascending mesolimbic cholinergic system, they signal aversive (unpleasant) state and induce aversive state in the receivers, while the 50 kHz vocalizations are initiated by the activity of the ascending mesolimbic dopaminergic system, they signal appetitive (pleasant) state and induce appetitive state in the receivers. Functional equivalents of these vocalizations in humans would represent signals of crying or laughter with similar consequences. Ethotransmission may play a facilitating and coordinating role in social behavior. Broader significance of ethotransmission and its adaptive or maladaptive role in social behavior will be discussed. Research supported by Natural Science and Engineering Research Council of Canada.

Alarm and appeasing pheromones in rats. Yasushi Kiyokawa1. 1Laboratory of Veterinary Ethology, The University of Tokyo, Tokyo, Japan. It is well known that many animals have highly developed olfactory systems and are highly dependent on their olfactory system. With developed olfactory systems, animals advertise their physiological state, including health status and reproductive availability, to other conspecifics using olfactory signals. A subset of olfactory signals that induces a stereotypical reaction,

including a definite behavior and/or physiological change, has been called pheromones. In addition to these classical pheromones, research has suggested the existence of pheromones that can modulate a wide variety of responses by activating/suppressing a neural circuit related to emotional responses. Here I will briefly introduce 2 types of "ethotransmissions" mediated by pheromones in rats. In alarm pheromonal communication, rats release 4-methylpentanal and hexanal from their perianal region when they are stressed. These molecules activate the anxiety circuit, including the bed nucleus of the stria terminalis, when 4-methylpentanal and hexanal are simultaneously detected by the vomeronasal system and the main olfactory system, respectively. Consequently, recipient rats show a variety of anxiety responses, depending on the threatening stimuli. In appeasing pheromonal communication, non-stressed rats release an appeasing pheromone, which is detected by the main olfactory system of recipient rats. When detected, this pheromone suppresses activation of the fear circuit, including the basolateral complex of the amygdala. As a result, appeasing pheromone ameliorates fear and stress responses elicited by a variety of aversive stimuli. The higher the animal has evolved, the more complex life the animal lives. In such situations, pheromones that modify the emotional circuit, rather than evoke a specific stereotypical response, may be effective transmitters to induce an appropriate response depending on the situation. Therefore, ethotransmission may contribute to increase inclusive fitness in animals. All the studies were supported by JSPS KAKENHI.

Ultrasonic vocalization in behavioral paradigms of innate and learned fear. Markus Fendt (1,2), Jorge R Bergado Acosta (1), Marcel Brosch (3), Evelyn Kahl (1), Kerstin Wernecke (1) & Markus Wöhr (4). (1) Institute for Toxicology and Pharmacology, (2) Center of Behavioral Brain Sciences, (3) Integrative Neuroscience Program, Otto-von-Guericke University Magdeburg, Germany. (4) Behavioral Neuroscience, Experimental and Physiological Psychology, Philipps-University of Marburg, Germany. Rats emit 22-kHz calls in aversive situations such as exposure to a predator. Here, we investigated the ability of different innate and learned stimuli to induce or inhibit 22-kHz calls. In our first experiment, we asked whether predator odors, i.e. stimuli predicting a predator, also induce 22-kHz calls. Rats were exposed to two different natural predator odors (urine samples of lions and foxes), to an artificial predator odor (TMT), or to water (control). During odor exposure, defensive behavior and ultrasonic vocalization were recorded. Both predator odors as well as TMT induced different behavioral changes such as risk assessment, avoidance and freezing. Interestingly, exposure to both predator odors but not to water and TMT induced 22-kHz calls in a small proportion of the rats. These calls were very similar to 22-kHz calls recorded in fear conditioning experiment but mean duration was significantly shorter. However, playback tests demonstrated that these 'short' 22-kHz calls are able to induce avoidance behavior in conspecifics. In a second experiment, we investigated whether learned signals predicting safety or relief from an aversive event affect the emission of 22-kHz calls. Four groups of rats were fear conditioned, safety conditioned, relief conditioned or sham conditioned. One day later, the animals were exposed to the conditioning context, to startle stimuli, and to the fear, safety, relief CS or sham CS. The conditioning context and startle stimuli induced 22-kHz calls in most animals. The safety CS robustly and the relief CS modestly reduced the number of 22-kHz calls, whereas the fear and sham CS had no effects. In current experiments, we expose pairs of rats to fear and/or safety CS and measure defensive behavior and ultrasonic vocalization. Together, our study shows that 22-kHz ultrasonic vocalization is modulated by a variety of environmental stimuli. Funding: German Science Foundation (DFG), SFB779/B13.

16:00-18:00 **Symposium: Drugs of abuse? Beyond the pharmacological reinforcement.** Chairs: Christian Müller and Klaus Miczek. *Setouchi Hall, Room 1-2*

Lipid systems mediate the selective antidepressant effects of self-administered alcohol in rodent models. Christian P. Müller, Friedrich-Alexander-University of Erlangen-Nuremberg, Germany. Alcohol is a major psychoactive drug in western societies involved in many cultural activities. It was shown that alcohol can be instrumentalized, i.e. used to achieve goals that would be impossible to achieve or require more work load without alcohol use. Alcohol use can serve numerous instrumentalization goals, one of the most important goals being the self-medication for innate or induced psychiatric problems, like for depression and/or anxiety disorders. While the neuropharmacology of alcohol is well known, neurobiological mechanisms for alcohol instrumentalization are poorly understood. Together with cholesterol and glycerophospholipids, sphingolipids are the most common lipids in brain membranes. Sphingolipids form lipid rafts and signaling platforms, which are membrane compartments enriched in G-protein-coupled receptors. Acid sphingomyelinase (ASM) hydrolyses sphingomyelin to ceramide and phosphorylcholine and, thus, represents a major regulator of sphingolipid metabolism. We found that overexpression of ASM in mice (tgASM) not only induces depression-like behaviour, but also enhanced consumption of alcohol and the alcohol-deprivation-effect after repeated withdrawal in a free-choice drinking paradigm. Furthermore, we found that free-choice alcohol drinking, but not forced alcohol exposure, reduces depression-like behaviour selectively in depressed animals by normalization of ASM activity. Using SolariX MALDI-MS slice imaging, we found that ASM hyperactivity induces sphingolipid and subsequent monoamine transmitter allostasis in the nucleus accumbens. Alcohol drinking restores sphingolipid and monoamine homeostasis selectively in depressed mice. Here we provide first mechanistic evidence for alcohol instrumentalization with the goal to self-medicate and ameliorate behavioural symptoms of a genetically-induced innate depression. We show that alcohol drinking normalises ASM function and re-establishes sphingolipid- and monoamine homeostasis in the nucleus accumbens of depressed mice. Thus, sphingolipid homeostasis emerges as a new mechanism to control depression-alcohol addiction comorbidity. This work was supported by funding from DFG, MU 2789/8-1, and by funding from the Interdisciplinary Center for Clinical Research (IZKF) Erlangen, Project E13.

Explaining how the drug, the set and the setting interact to generate different patterns of drug choice in rats. Serge H Ahmed1,2. 1Université de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, 146 rue Léo-Saignat, F-33000 ;2 Bordeaux, France; 2CNRS, Institut des Maladies Neurodégénératives, UMR 5293, 146 rue Léo-Saignat, F-33000 Bordeaux, France. Since the seminal work of Norman Zinberg and others, one knows that all the 3 big variables of drug use behavior – that is, the drug (i.e., the specific psychoactive effects of the substance used), the set (i.e., the individual features and history of the drug user), and the setting (i.e., the situations and contexts where drug use takes place and where the effects of the drug are experienced) – play a role in the transition to drug addiction. But one still incompletely understands how these different variables interact to trigger this transition in a given individual. Part of the reason for this ignorance is that these variables are generally studied separately, with little explicit consideration of the other variables and their interactions. We and others have over the past few years attempted to approach this problem in nonhuman animals given access to different drugs (i.e., cocaine, heroin) in different choice settings (e.g., intermittent versus continuous choice between drug or nondrug options). Overall, our research has led us to formulate a model that gives equal attention to and integrates drug, set, and setting variables as well as their interactions in explaining different patterns of drug choices. Notably, in the 3-D choice space defined by the drug, the set and the setting, we found regions of low or high vulnerability to develop exclusive and potentially self-destructive patterns of drug use. During my talk, I will lay out the empirical basis of this model and attempt to showcase its heuristic power, including for understanding the neurobiology of drug use and addiction. Funding

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The reinforcing effects of addictive drugs: it's all about location. Aldo Badiani1,2; Silvana De Pirro1,2. 1Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy; 2Sussex Addiction Research and Intervention Centre (SARIC), School of Psychology, University of Sussex, Brighton, UK. It is often thought that the reinforcing effects of all addictive drugs are essentially the same, and depend on the activation of dopaminergic systems of the brain, which result in a positive affective state. This presentation will discuss findings from animal and human studies that are incompatible with unitary models of drug reward. In particular, it will be shown that the subjective effects of heroin and cocaine in human addicts have very different, almost opposite, affective valence. Furthermore, it will be shown that the affective state induced by heroin and cocaine in addicts can be modulated in opposite directions by the setting of drug taking. Finally, fMRI data indicate that the ability of heroin and cocaine memories to activate the reward regions of the brain differ substantially as a function of setting. These findings are in agreement with results of self-administration and molecular biology experiments conducted in the rat. In conclusion, no attempt at simplification should ignore the fundamental role played by environmental factors in modulating the subjective and neurobiological effects of commonly used drugs.

The CRF system and brief episodes of aggression and defeat: Behavior in Excess. Klaus A. Miczek, Herbert Covington III, Xiao Han, Michael Leonard and Joseph F. DeBold. Departments of Psychology, Pharmacology, Psychiatry and Neuroscience, Tufts University, Medford and Boston, MA. Corticotropin releasing factor (CRF) signalling in the ventral tegmental area (VTA) and dorsal raphe nuclei (DRN) has emerged to be important in extra-hypothalamic microcircuits for social stress. We have characterized the functional role of intra-VTA and intra-DRN CRF and CRF receptors in aggressive and defeated mice and rats before and after confrontations. (1) In protection experiments, we microinjected CRF R1 and R2 antagonists prior to each aggressive or defeat episode. CRF R1 antagonists prevented the robust aggressive arousal prior to each aggressive confrontation. (2) Cre-dependent DREADD expression in CRF transgenic C57BL/6J mice allows for examining the activational role of CRF in DRN and VTA. Responding in anticipation of sex, aggression or exercise is prevented by CRF R1 antagonism, and we propose a similar pattern of effects in anticipation of escalated drug taking, but possibly via different microcircuits. (3) Assays of CRF in microdialysis samples from the VTA reveal increased release in anticipation of aggressive confrontations in aggressors as well as in reaction to social defeat stress in victims of aggression. We speculate that the expression of mRNA for CRF and CRF receptors will reveal persistent profiles of neuroplasticity after exposure to brief episodes of escalated aggressive behavior or social defeat stress. (4) The role of CRF in social defeat stress is evident in the induction and expression of intensified cocaine seeking and taking in mice and rats. Microinjections of CRF agonists and antagonists in the VTA regulate patterns of binge-like cocaine intake. We hypothesize that the persistent plasticity in discrete extrahypothalamic CRF circuits contribute to species-normative, excessive and maladaptive behavioural patterns.

18:30- 20:30 **Poster Session 1.** *Setouchi Hall, Room 3-5*

1. **Age-related neuroinflammatory responses associated with changes in learning impairments in a mouse model of Alzheimer's disease**. Shenghua Zhu1,2, Jun-Feng Wang1,2, Xin-Min Li3.

1Department of Pharmacology and Therapeutics, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, 2 Kleysen Institute for Advanced Medicine, Health Sciences Centre, Winnipeg, MB, Canada, 3 Department of Psychiatry, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada. In Alzheimer's disease (AD), both amyloid deposition and neuroinflammation appear in the early course and become notably conspicuous as disease progresses. However, the progression of neuroinflammation and its relationship with amyloid deposition and behavioural changes have not been characterized as many underlying mechanisms rarely occur in isolation. Methods: The present study will thoroughly characterize the behaviour of the APP/PS1 mouse model of AD, using a comprehensive test battery designed to assess a variety of behaviours. Using a cross-sectional design, these behaviours will be assessed in mice at different ages. Brain pathology measures for amyloid deposition and neuroinflammation are done post-mortem. Results: APP/PS1 mice exhibited significant learning deficits from the age of 5 month, which were aggravated at the later stages of life. However, the degree of memory impairment plateaus after 12 months. Histological analyses showed that an early appearance of amyloid plaques at 3 months of age with a linear progressive increase up to 22 months. This pronounced amyloid deposition was accompanied by a steady increase of the glial fibrillary acidic protein (GFAP) positive astrocytes and CD11b positive microglia up to the age of 9-12 months. Interestingly the expression levels of GFAP rose steeply from the age of 5 months to the age of 9 months and then stabilized at the age of 12 months which coincided with the observed pattern of learning deficits in APP/PS1 mice. Conclusions: These findings provided evidence that neuroinflammation might be involved in the development and progression of cognitive deficits in APP/PS1 mice, suggesting novel intervention and prevention strategies for AD.

2. **Up-regulation of astrocyte-derived immune-related genes contributes to behavioral impairment.** Norimichi Itoh1, Taku Nagai1, Akira Sobue1, Daisuke Ibi2, Akira Nakajima3, Toshitaka Nabeshima4, Kiyofumi Yamada1. 1Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Nagoya, Japan. 2Department of Chemical Pharmacology, Faculty of Pharmaceutical Science, Meijo University, Nagoya, Japan. 3Department of Drug Safety Science, Nagoya University Graduate School of Medicine, Japan. 4Advanced Diagnostic System Research Laboratory, Fujita Health University Graduate School of Health Science, Toyoake, Japan. Environmental factors such as virus infection during prenatal period, low birth weight, and hypoxia increase the vulnerability for neuropsychiatric disorders. Epidemiological studies showed that maternal infection during the pregnancy has been associated with the increased risk of mental disorders in the offspring. However, little is known about the neurodevelopmental mechanism underlying the association between perinatal infection and brain dysfunction in later life. To clarify the mechanism, we have developed a mouse model of viral infection during the perinatal period using polyriboinsinic-polyribocytidylic acid (poly I:C). Mice treated with poly I:C at postnatal day2 to 6 showed schizophrenia-like behavioral abnormalities in adulthood, such as increased anxiety, memory impairment, and social behavior deficit. We also showed that poly I:C-dependent immune reaction upregulates a variety of gene expression. Among them, we focus on two molecules, interferon-induced transmembnrane protein 3 (IFITM3) and major histocomatibility complex class I (MHCI). Poly I:C treatment induced the expression of IFITM3 in astrocytes but not in neurons. Condition medium derived from poly I:C-treated astrocytes suppressed neurite outgrowth and spine formation in primary cultured neurons. This pheotype was rescued by depletion of IFITM3. We screened IFITM3-

interacting proteins by proteomic approach. We identified the RabGDI, one of the regulators of Rab small GTPases, as a novel IFITM3-interacting protein. We confirmed the interaction of IFITM3 with RabGDI by pull down assay. Expression of IFITM3 on COS7 cells showed increased size of EEA1-positive vesicles. The same phenotype was observed in the poly I:C-treated astrocytes. These results suggest that IFITM3 regulates intracellular transport through RabGDI.Because immune response and inflammatory reaction such as poly I:C treatment increase the expression of MHCI, we also investigated the role of MHCI in astrocytes. Astrocyte specific expression of MHCI under the control of GFAP promoter showed some behavioral defects including cognitive impairments in novel object recognition test, pre-pulse inhibition test, and methamphetamine-induced hyperlocomotion. Expression of MHCI in astrocytes increased the number of microglia and decreased parvalbumin-positive neurons. Moreover, astrocyte specific expression of MHCI decreased the spine density in the medial prefrontal cortex of mice. These results suggest that astrocyte-derived MHCI attributes to the pathophysiology of psychiatric disorders. Taken together, our findings support the idea that molecules involved in immune and inflammatory responses may contribute to the pathophysiology of psychiatric disorderss such as schizophrenia.

3. **Behavioral characterization of Neuropeptide S receptor - deficient mice in animal paradigms of pathological fear.** Kolodziejczyk Malgorzata H. 1, Fendt Markus1,2. 1Institute for Pharmacology and Toxicology, 2Center of Behavioral Brain Sciences, Otto-von-Guericke University Magdeburg, Germany. Dysfunctions within mechanisms underlying fear can lead to anxiety disorders (AD) characterized by inadequate anxiety states and generalized fear learning. The neurobiological underpinnings of most AD are as yet not clear. Moreover, treatments aren´t optimal due to limited efficiency and side-effects. Neuropeptide S (NPS), that has been shown to exert strong anxiolytic effects in rodents, seems to be a promising target for AD. Several clinical studies identified the association between a polymorphism in the NPS receptor (NPSR) gene with an increased incidence of AD. Consequently, we hypothesize that NPSR-deficient mice will be more prone to develop AD. To study the interaction between NPSR deficiency and AD NPSR-/- mice were submitted to two different behavioral paradigm developed to investigate (a) generalized fear as observed in post-traumatic stress disorders (PTSD) or (b) panic-like anxiety. In 1st approach NPSR-/- mice were fear-conditioned (FC) with injection of corticosterone (CORT). One day and one month after FC animals were tested for their fear memory. During tests animals were exposed to a novel, a similar and the conditioning context to assess the generalization of the contextual fear memory. To determine the CORT level blood samples were collected. Also, brains slides were analyzed for neuroinflammatory changes. In 2nd approach NPSR-/- mice were treated with sodium lactate (SL) that has been shown to induce panic-like anxiety in panic-prone animals/humans. Animals were tested for their social communication deficit (sociability test) and anxiety level (light/dark box test, CORT level). NPSR-/- mice appear to be more prone to develop PTSD-like fear memory 4 weeks after a traumatic event. Also, high CORT levels during FC seem to be associated with impaired context discrimination. However, in the 2nd paradigm genotype appears to play a minor role. SL effects are highly dependent on individual baseline anxiety of the mice. We postulate that NPSR deficiency is associated with a higher probability to develop PTSD-like fear, though, seems to not lead to panic behavior. Support: DFG (FE 483/7-1).

4. **Neuromodulatory effect of cytokine in the dorsal raphe nucleus and individual difference of aggression**. Aki Takahashi1,2,3, Hossein Aleyasin2, Meghan E. Flanigan2, Anna Brancato2, Caroline Menard2, Madeline L. Pfau2, Veronika Kana2, Wang Jun2, Georgia E. Hodes2, Bruce S. McEwen3 and Scott J. Russo2. 1Laboratory of Behavioral Neuroendocrinology, University of Tsukuba, 2Icahn School of Medicine at Mount Sinai, 3The Rockefeller University. Interleukin-1 beta (IL-1β) is a pro-inflammatory cytokine that produces fever and sickness behaviors, and IL-1β has also been implicated in several psychiatric disorders. Human studies have shown that the level of IL-1β in periphery or cerebrospinal fluid correlates with aggression trait. In this study, we aimed to study the role of IL-1β on the individual difference of aggression using mouse model. Outbred CD-1 mice show individual differences in aggressive behavior with 70 % of animals always showing territorial aggression (termed Aggressors: AGG) and 30 % exhibiting no aggressive behavior at all (termed non-aggressors; NON). When we measured peripheral cytokines, there was a phasic increase of IL-1β in the blood by the aggressive encounter in both AGG and NON; however, there was no difference between groups. By contrast, we found significant higher level of central IL-1β in the dorsal raphe nucleus (DRN) in NON compared to AGG. To examine the role of IL-1β in the DRN, we injected a IL-1 receptor antagonist into either lateral ventricle or directly into the DRN. Our result showed that both i.c.v. injection and intra-DRN microinjection of IL-1 receptor antagonist increased aggressive behavior. Previous studies have shown that IL-1b can change neural activation and suppress serotonin (5-HT) neuron activity in the DRN by activating GABA interneurons. c-Fos immunohistochemistry showed that AGG showed higher c-Fos activation in the 5-HT neurons than NON in medial aspect of dorsal raphe nucleus. These result suggests that IL-1 receptor mediated pathway in the DRN has an inhibitory role on aggressive behavior by modulating 5-HT neuron activity.

5. **Stress-induced alcohol drinking in mice lacking -opioid receptors**. Yuki Moriya 1.2; Yoshiyuki Kasahara 2.3; F. Scott Hall 4; George R. Uhl 5; Kazutaka Ikeda 1; Ichiro Sora 6. 1. Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan. 2. Dept. of Biological Psychiatry, Tohoku Univ. Graduate School of Medicine, Japan. 3. Dept. of Disaster Psychiatry, International Research Institute of Disaster Science, Tohoku University, Japan. 4. Dept. of Pharmacology, Toledo Univ. Pharmacy and Pharmaceutical Sciences, USA. 5. Molecular Neurobiology Branch, Intramural Research Program, National Institute on Drug Abuse, USA. 6. Dept. of Psychiatry, Kobe Univ. Graduate School of Medicine, Japan. One prevalent theory is that stress increases alcohol consumption because alcohol relieves the psychological and physiological outcome of stress, such as anxiety or physical pain. A complex relationship exists between alcohol-drinking behavior and stress. There are well-known sex differences in the epidemiology of alcohol dependence; however, the relationship between stress and alcohol consumption is poorly understood. There obviously exist sex differences in sensitivity, perception, and responsiveness to stress, and then these differences will be reflected in drinking behavior. Genetic factors, such as differences in genes for μ-opioid receptor (MOP) systems, also have a substantial influence on alcohol consumption, but only a limited set of such genetic influences on stress-induced alcohol consumption have been examined. The current studies investigated the influence of MOP deletion on voluntary ethanol consumption in female wildtype (WT) and knockout (KO) mice after chronic restraint stress or long-term social isolation stress. This study assessed the effects of isolation-rearing or restraint stress on later ethanol intake using a two-bottle home-cage consumption (ethanol 8% vs. water) paradigm in female WT and MOP gene KO mice. While restraint stress did not affect ethanol consumption in MOP-KO female mice, it

produced a reduction in ethanol consumption in WT mice. Socially-reared MOP-KO female mice consumed more ethanol than female isolation-reared MOP-KO, female socially-reared WT, or female isolation-reared WT mice. Stress affected ethanol drinking behavior in female mice, but the nature of these effects was dependent on the stressor examined. Acknowledgements: Grant-in-Aid for Research Activity start-up: 16H07463, Japan Society for the Promotion of Science (JSPS): 254961, The Ministry of Education,Culture,Sports,Science and Technology(MEXT).

6. **Resilience Factors Mediating Social Defeat Stress in Syrian Hamsters**. Chris M. Markham1, Malcolm Edwards1, Tiara Lacey2, Janae Best2, Michael Smith1. 1Department of Psychology, Morehouse College, Atlanta, GA. 2Department of Biology, Spelman College, Atlanta, GA. Our lab utilizes an ethologically relevant model of social stress whereby defeated Syrian hamsters exhibit long lasting changes in behaviors, including increased submissiveness and a complete lack of territorial aggression, even when paired with a smaller, non-aggressive intruder (NAI). A small subset of hamsters, however, appears to be resilient to the effects of this defeat experience. Several lines of evidence suggest that various resilience factors may function to ameliorate the effects of traumatic stress, but many of these studies have used non-ethological models such as electric shock or variable stress. The present series of experiments examined two putative resilience factors, neuropeptide Y (NPY) and voluntary exercise, on social defeat stress. In Experiment 1, we examined a) whether intracerebroventricular (icv) infusion of NPY can induce a state of behavioral resilience in socially defeated hamsters by reducing submissive behaviors upon exposure to a NAI and b) whether these effects are mediated by the NPY Y1 receptor. Results show that icv infusion of NPY significantly reduced the expression of submissive behaviors in defeated hamsters and that pretreatment with the NPY Y1 receptor antagonist BIBP 3226 followed by an infusion of NPY counteracted this effect by causing a re-emergence of submissive behaviors. In Experiment 2, we examined whether voluntary exercise in the form of free access to a running wheel can inhibit the effects of social defeat. Socially defeated hamsters were divided into the exercise (EX) or no-exercise (NEX) groups and exposed to a running wheel or standard cage enrichment for two weeks. Following the EX or NEX period, all subjects were socially defeated and tested with a NAI. Our data indicate that hamsters in the EX group exhibited significantly lower levels of submissive behaviors compared to the NEX group, indicating that voluntary exercise promoted resilience to social defeat stress. Together, these results suggest that NPY and voluntary exercise may promote stress resilience in socially defeated hamsters. Future studies will examine whether there is an interaction between these factors. Funding: National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R25GM060566.

7. **Impaired visual discrimination learning in Disc1-knockout mice, reversed by clozapine treatment**. Bolati Wulaer1, Taku Nagai1, Akira Sobue1, Keisuke Kuroda2, Kozo Kaibuchi2, Toshitaka Nabeshima3, Kiyofumi Yamada1. 1)Department of Neuropsychopharmacology and Hospital Pharmacy, 2)Department of Cell Pharmacology, Nagoya University Graduate School of Medicine. 3)Advanced Diagnostic System Research Laboratory, Fujita Health University, Graduate School of Health Science and Aino University. Disrupted-in-schizophrenia 1(DISC1) is a promising candidate susceptibility gene for a spectrum of psychiatric illnesses that share cognitive impairments in common, including schizophrenia, bipolar disorder and major depression. In our previous study, we have generated mice lacking exons 2 and 3 of the Disc1 on a C57BL/6J genetic background (Disc1Δ2-3/Δ2-3 mice). Here we

investigated cognitive function of Disc1Δ2-3/Δ2-3 mice in a translatable touchscreen-based visual discrimination and subsequently reversal learning task to evaluate the complex measures of operant learning and cognitive flexibility. Furthermore, marble-burying and nestlet shredding tests were conducted for further characterization of repetitive and compulsive-like behaviors. Disc1Δ2-3/Δ2-3 mice required significantly more trials to reach the 80% correct response criterion in the visual discrimination task, which was mainly due to high perseverative response compared to wild-type animals. There was no difference in the reversal learning. Moreover, Disc1Δ2-3/Δ2-3 mice exhibited a significant increase in the number of marbles buried in a marble bury test and shredded more nestlets in a nestlet shredding test compared with wild-type mice. During the training, the daily treatment of clozapine ameliorated the impairment by normalizing the preservative behavior in visual discrimination task and reversed the abnormal burying behavior in marble bury test. Our findings indicate that Disc1Δ2-3/Δ2-3 mice exhibit profound repetitive and compulsive-like behaviors, which could be ameliorated by treatment with clozapine.

8. **The effects of synthetic psychoactive cathinones on lethality and temperature**. Dawn Muskiewicz, F. Scott Hall, Yasir Saber, Federico Resendiz Gutierrez. Department of Pharmacology and Experimental Therapeutics, The University of Toledo College of Pharmacy and Pharmaceutical Sciences, Toledo, OH, USA. Synthetic psychoactive cathinones (SPCs) are drugs with psychostimulant and entactogenic properties similar to methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA). Abuse of SPCs is a substantial public health problem associated with adverse events, emergency room admissions, and lethal overdoses, although there is uncertainty as to whether all drugs in this class share similar risks, and whether those risks are greater than those associated with METH or MDMA. Hyperthermia is an important factor in the lethal and neurotoxic effects of METH and MDMA, but its importance for the adverse effects of SPCs is not known. In a recent study, we found that the SPC methylone (2-methyamino-1-[3,4-methylenedioxy-phenyl]propan-1-one) had an LD50 that was slightly lower than that observed for METH or MDMA. Lethality has not been examined for most other SPCs. LD50 studies were performed for the SPCs cathinone, methcathinone, methylenedioxypyrovalerone (MDPV), and mephedrone, as well as MDMA and METH. Subjects were adult male and female C57BL/6J mice. After acclimatization to a test chamber and establishment of baseline temperature for 1 hour, subjects were injected with 0-120 mg/kg (base) IP of a test drug; 6 doses were tested for each drug; N=5 male and N=5 female subjects per condition. Temperature was measured at 20 minute intervals for 2 hours. Behavioral observations (e.g. hyperlocomotion, seizure, 5-HT behavioral syndrome, etc.) were also made for each interval. LD50 values for METH and MDMA were similar to previously reported values, 84.1 and 92.2 mg/kg respectively. Pronounced locomotor activity was observed at the lowest doses, and replaced by stereotypy at higher doses. Slight hyperthermia was observed at some doses. At high doses convulsions and death occurred within minutes. The LD50 for mephedrone was 105.4 mg/kg; convulsions and death similarly occurred within minutes at the highest dose. By contrast, neither lethality nor convulsions were observed for MDPV, cathinone, or methcathinone at doses up to 120 mg/kg IP. Moreover, in contrast to METH and MDMA, pronounced dose-dependent hypothermia was observed for mephedrone, MDPV, cathinone and methcathinone – a reduction of 7-8 °C for some doses. None of the SPCs studied here (MDPV, mephedrone, cathinone or methcathinone) had LD50 values that were lower than METH or MDMA. Similar to METH and MDMA, the highest dose of mephedrone induced lethality that was associated with convulsions. However, unlike those drugs, mephedrone reduced body temperature. Even more

pronounced hypothermia was observed with cathinone, methcathinone and MDPV, but was not associated with lethality. These data indicate that: (1) not all SPCs exhibit greater lethality than METH and MDMA (at least under the conditions studied here); (2) SPCs differ substantially in their effects on thermoregulation; (3) as we have previously found for methylone, effects of SPCs on temperature appear to be independent of effects on lethality.

9. **Animal models of maternal immune activation and relevance for schizophrenia**. Harms L,1, Meehan C1, Dunn A1, Hodgson D1, Michie P1. 1Priority Research Centre for Brain and Mental Health Research, University of Newcastle, Callaghan, NSW, Australia. Exposure to infection during gestation has been shown to increase risk for developing schizophrenia in offspring. Bacterial or viral mimetics have been administered to pregnant rodents to create animal models of 'maternal immune activation' (MIA) and have demonstrated that immune stimulation during gestation is associated with a range of schizophrenia-related changes to brain development and behaviour in rat and mouse offspring. To further investigate the impact of MIA on schizophrenia-related behaviour as well as electrophysiological 'biomarkers' for schizophrenia, we investigated the impact of MIA (via Poly (I:C) injection) at mid (Gestational day, GD, 10) and late (GD19) gestation rat offspring. Regardless of GD of exposure, rats exposed to MIA had reductions in prepulse inhibition. In addition, rats exposed to MIA on GD19, but not GD10, exhibited transient working memory impairments. While MIA-exposed rats did not exhibit changes in mismatch negativity or spontaneous oscillatory activity, stimulus-driven gamma oscillations were impaired in MIA rats, similar to patients with schizophrenia. These findings indicate that the MIA rat model is a highly relevant model for the investigation of the behavioural and neurobiological correlates of aberrant gamma oscillations.

10. **The inferior colliculus: An alternative structure for deep brain stimulation in Parkinson's Disease?** Karl-Alexander Engelhard, Rainer K. W. Schwarting, Liana Melo-Thomas. Behavioral Neuroscience, Experimental and Biological Psychology, Philipps-University of Marburg, Gutenbergstr. 18, 35032 Marburg, Germany. The inferior colliculus (IC) is widely known as a midbrain auditory relay station. Additionally, IC has also been implicated in processing sensory-motor responses as demonstrated in the animal model of haloperidol-induced catalepsy. High-frequency (830Hz) deep brain stimulation (DBS) of the rat IC reduces haloperidol-induced catalepsy, which models akinesia of Parkinson`s disease, but clinical implication of this DBS type is limited since it is aversive. However, typical DBS stimulation frequencies range between 30-130Hz. We therefore asked whether low-frequency (30Hz) DBS of the IC can improve catalepsy without aversive side effects. Young adult rats were implanted with a stimulation electrode unilaterally into the central nucleus of the IC. We determined individual escape threshold intensities during 830Hz DBS of the IC and then assessed the effects of 5min sub-chronic 30Hz DBS at individual escape thresholds on haloperidol-induced catalepsy (0.5mg/kg, i.p.) compared to a sham-stimulated control. We further assessed possible aversive side effects of our stimulation protocol in a conditioned place preference (CPP) test, using 4 conditioning trials. Sub-chronic 30Hz DBS of the IC strongly ameliorated haloperidol-induced catalepsy without any evidence of aversive behavior induced by the stimulation. In fact, in the CPP test we found that the preference for the 30Hz DBS-paired side increased after conditioning, indicating that our stimulation protocol was appetitive. The results show that the IC can serve as an alternative target for DBS in Parkinson's disease. DBS targeted at the IC might be even effective in reducing comorbid depression-related symptoms.

11. **Ultrasounds release catalepsy in rats: A new animal model for paradoxical kinesia**. Luan Castro Tonelli, Markus Wöhr, Rainer K. W. Schwarting, Liana Melo-Thomas. Behavioral Neuroscience, Experimental and Biological Psychology, Philipps-University of Marburg, Gutenbergstr. 18, 35032 Marburg, Germany. Paradoxical kinesia refers to a sudden transient ability of akinetic patients to perform motor tasks they are otherwise unable to perform. The mechanisms underlying this phenomenon are unknown due a paucity of valid animal models that faithfully reproduce paradoxical kinesia. Here, we present a new method to study paradoxical kinesia by "awakening" cataleptic rats through presenting appetitive 50-kHz ultrasonic vocalizations (USV), which are typical for social situations with positive valence, like juvenile play or sexual encounters ("rat laughter"). Rats received systemic haloperidol to induce catalepsy, which was assessed by means of the bar test. During that test, they received playback presentations of 50-kHz USV, time- and amplitude-matched white noise (NOISE), background noise (BACKGROUND) or SILENCE. Only when exposed to appetitive 50-kHz USV, the otherwise cataleptic rats rapidly started to move efficiently, and most of them even walked towards the stimulus source. In a second experiment, we provide first evidence for a possible brain mechanism of this effect. We selected the inferior colliculus as a target since it is known to serve not only as an acoustic relay station, but can also modulate haloperidol-induced catalepsy. We found that intracollicular microinjection of NMDA prevented the effectiveness of 50-kHz USV to induce paradoxical kinesia without blocking basic acoustic processing. Together, our research not only provides a completely new animal model to study mechanisms of paradoxical kinesia, but also hints at specific brain mechanisms through which such effects might be exerted.

12. **Involvement of dopamine and norepinephrine in the sex-specific regulation of social play by vasopressin**. Remco Bredewold1,2, Nara F. Nascimento2, Alexa H. Veenema1,2. 1Neurobiology of Social Behavior Laboratory, Department of Psychology, Michigan State University, East Lansing, MI, USA. 2Neurobiology of Social Behavior Laboratory, Department of Psychology, Boston College, Chestnut Hill, MA, USA. Social play is an affiliative and rewarding behavior displayed by nearly all mammals and peaks during the juvenile period. We recently showed that arginine vasopressin (AVP) acting via the V1a receptor (V1aR) within the lateral septum (LS) regulates social play in opposite directions in male and female juvenile rats. The LS receives dopaminergic input from the ventral tegmental area and norepinephrinergic input from the locus coeruleus. Therefore, we sought to determine whether AVP interacts with dopamine (DA) and/or norepinephrine (NE) to regulate social play behavior in sex-specific ways. Using retrodialysis combined with microdialysis in awake and freely moving juvenile rats, we found that exposure to social play increased DA release in the LS of females, but not of males. Interestingly, V1aR blockade in the LS abolished this sex difference in DA release during social play. In contrast to DA release, exposure to social play did not alter NE release in the LS of either sex. However, V1aR blockade in the LS caused an increase in NE release in the LS of females but not of males. These findings suggest that the sex-specific regulation of social play by the LS-AVP system involves differential monoaminergic neurotransmission in the LS of male and female juvenile rats. Using pharmacological manipulations, we currently determine the causal involvement of DA and NE released in the LS in the sex-specific regulation of social play by AVP. This research was supported by NIMH R01MH102456 to AHV.

13. **Blockade of the sigma-1 chaperone impairs brain plasticity induced in mice by habituation to a complex environment, the Hamlet test**. Lucie Crouzier, Olivier Teuf, Anaïs Rivière, Tangui Maurice. Inserm U1198, University of Montpellier, 34095 Montpellier France. The σ1 receptor is a membrane-associated protein expressed in neurons, astrocytes, oligodendrocytes and microglia. It is tightly expressed at mitochondria-associated endoplasmic reticulum (ER) membranes (MAM), complexing the glucose-related protein 78/binding immunoglobulin protein (BiP). Upon cellular stress or via agonist stimulation, σ1 receptor dissociates from BiP and binds inositol 1,4,5-trisphosphate (IP3) receptor, enhancing calcium entry into mitochondria. It can also translocate to plasma membrane and modulate the activity of numerous ionophores and receptors for neurotransmitters and trophic factors. The σ1 receptor shapes cellular plasticity also by directly modulating the activity of pleiotropic transcription factors, such as NFKB, CREB or c-fos, involved in the modulation of pro- and anti-inflammatory genes, cell death and survival. The σ1 receptor-mediated neuromodulation, affecting several cellular pathways has an important role on brain plasticity, response to stress, learning and memory, and neuroprotection. For instance, its activation potentiates long-term potentiation, neurite outgrowth and hippocampal neurogenesis. We here analyzed its impact on brain plasticity induced by habituation to a complex enriched environment (EE). The Hamlet test is a novel behavioral analysis appliance, fully automatized (ViewPoint), that provides a complex environment for testing topographical memory and spatio-temporal disorientation in mice. The apparatus mimics a small village with a central agora and streets expanding from it, leading to functionalized houses (Drink, Eat, Play, Run, Interact). EE is induced by habituating animals in the Hamlet, in groups of 6/8 individuals, during 4 h a day, for several weeks. Memory can be tested by depriving mice from water and testing their ability to locate the Drink house. Several groups were analyzed in parallel (non-habituated; habituated; habituated and repeatedly administered with NE-100, a selective σ1 antagonist) and the expression and activity of the σ1 receptor were analyzed after habituation. The antidepressant and anti-amnesic effect of selective σ1 agonists, the hippocampal neurogenesis and trophic factor levels were analyzed. We report that the pharmacological inactivation of σ1 receptor following NE-100 treatment prevented topographic memory, resistance to forced swimming and increased neurogenesis induced by habituation. The data showed that σ1 receptor activity plays a major role in the consequences of EE and therefore suggest that MAM physiology is impacted by EE. Funding: This study was funded by a SATT AXLR (Montpellier, France) maturation grant.

14. **Transgenic approaches to regulate the neuronal activity in rat vasopressin neuron**. Yoshimura Mitsuhiro, Maruyama Takashi, and Ueta Yoichi. Department of Physiology, School of Medicine, University of Occupational and Environmental Health, Japan. Rapid developments in optogenetic or chemogenetic approaches give us new insight in the field of neuroscience. Although there are several ambitious studies to express light-sensitive protein, channelrhodopsin 2 (ChR2), or specific drug-sensitive protein, designer receptors exclusively activated by designer drug (DREADD), by viral transfection techniques have been performed on oxytocin neurons and their axon terminals, to our knowledge, there is no successful study on arginine vasopressin (AVP) neurons using these techniques. We generated a transgenic rat that expresses the AVP-ChR2-enhanced green fluorescent protein (eGFP) fusion gene in the magnocellular neurosecretory cells (MNCs) of the hypothalamus. The eGFP fluorescence which indicates the expression of the ChR2 gene was observed in the supraoptic nucleus (SON) and the magnocellular division of the paraventricular nucleus (PVN). The intensities of eGFP fluorescence in those nuclei and posterior pituitary showed marked increased after

chronic salt loading (2% NaCl to drink for 5 days). Confocal laser scanning microscopic observation revealed that ChR2-eGFP was localized mainly in the membrane of MNCs. Whole-cell patch-clamp recordings were performed from a single MNC isolated from the SON of the transgenic rats and blue light evoked action potentials repetitively in a current clamp mode. We have also generated transgenic rat which expresses DREADD (hM3Dq) tagged with mCherry fluorescence under the downstream of the AVP promoter. The mCherry fluorescence which indicates the expression of the hM3Dq gene was observed in the SON and the magnocellular division of the PVN. The mCherry fluorescence were almost co-localized with AVP-like immunoreactivity (LI) positive neurons, and were not co-localized with oxytocin-LI neurons. The number of Fos-LI neurons which is the indicator of the neuronal activity was robustly increased in the AVP-LI neurons in the SON and PVN after administration of clozapine-N-oxide (CNO), which activates hM3Dq receptors specifically. We suppose to elucidate the role of endogenous AVP for various behavior, including drinking and feeding, using these transgenic rats.

15. **The effects of blocking nucleus accumbens dopamine D1-type receptors on social learning of food preferences in male and female mice.** Richard Matta1, Madison J. Russell1, Danielle J. Tessier1, and Elena Choleris1. 1Department of Psychology and Neuroscience Program, University of Guelph, Guelph, ON, Canada, N1G2W1. The neurotransmitter dopamine (DA) is involved in the regulation of numerous motivationally relevant behaviors, including drug-addiction, feeding, and social behavior. Previous work in our lab using systemic treatments has implicated D1-type (D1/D5) DA receptors in social learning and D2-type (D2/D3/D4) DA receptors in feeding behavior in the social transmission of food preferences (STFP) in mice (Choleris et al, 2011). The underlying brain region(s) of action mediating these effects are slowing being investigated. The ventral tegmental area has direct dopaminergic projections to many limbic brain regions, including the hippocampus and nucleus accumbens (NAc). Our previous studies using D1-type and D2-type DA receptor antagonists has shown that dorsal hippocampal D1-type and D2-type DA receptors mediate social learning in female mice, whereas only dorsal hippocampal D1-type receptors mediate social learning in males (Matta et al, 2014, 2016). NAc D1-type DA receptors have been strongly implicated in both social behaviours, and in individually acquired food preferences in rodents. Hence, the purpose of this study was to investigate the role of NAc D1-type DA receptors in the STFP in male and female mice. To do this, we microinfused the D1-type DA receptor antagonist SCH23390 (at 1, 2, and 4 µg/µL) directly into the NAc shell of adult male and female CD-1 mice. NAc infusions were 15 minutes before a 30 minute social interaction where mice had the opportunity to learn a food preference from a recently fed same-sex conspecific. Initial results show that the highest dose of SCH23390, at 4 µg/µL, blocked social learning. Furthermore, this social learning impairment could not be explained by any generalized changes in feeding behavior, since drug treatment did not affect total food intake. These results are consistent with those of our previous work using systemic treatments, and our intrahippocampal studies showing that D1-type DA receptors mediate social learning in the STFP. This study suggests that NAc D1-type DA receptors may also be regulating social learning in mice. Throughout, we will be highlighting sex differences, and possible effects of the estrous cycle on social learning. Supported by NSERC.

16. **Medial prefrontal cortex versus orbitofrontal cortex: teasing apart differences in plasticity after stress.** Samantha Adler1, Sarah Bulin2, Michael Patton1, Milena Girotti1, David Morilak1. 1University

of Texas Health San Antonio, San Antonio, TX, USA. Cognitive inflexibility is a symptom dimension shared by several stress-related psychiatric disorders; it contributes to their etiology and is exacerbated by stress, and yet it is poorly treated by current medications. To create better treatments, we need to know more about the neurobiology of stress effects on this symptom. In rodents, the attentional set-shifting task (AST) can be used to evaluate two types of cognitive flexibility: reversal learning, which is mediated by the orbitofrontal cortex (OFC), and extra-dimensional set-shifting, which is mediated by the medial prefrontal cortex (mPFC). We have identified two types of chronic stress that elicit deficits in each of these functions: chronic intermittent cold (CIC) stress impairs reversal learning ($p<.01$), while chronic unpredictable stress (CUS) impairs extra-dimensional set-shifting ($p<.05$). In recent work, we have found that each stress paradigm affects the output of the two brain regions very differently. Field potentials evoked acutely in the OFC by mediodorsothalamus (MDT) afferent stimulation in rats were potentiated after 2 weeks of CIC stress compared to baseline (before stress) ($p<.01$). Conversely, MDT-evoked responses in the mPFC were decreased after two weeks of CUS ($p<.001$). Since changes in excitatory transmission are often accompanied by morphological changes in dendrites, we are now analyzing the differences in dendritic arborization and spine density after stress by using Golgi staining. We expect stress-induced hyperactivity in the OFC to be associated with dendritic elaboration and increased spine density, and hypoactivity in the mPFC to be associated with dendritic retraction and decreased spine density. Finally, since changes in excitatory transmission correlate with altered AMPAR surface expression, we will also measure surface labeling of AMPAR subunits in the OFC and mPFC after chronic stress, anticipating that hyperactivity in the OFC is accompanied by increased AMPAR surface expression, while hypoactivity in the mPFC correlates with reduced AMPAR surface expression. This work was supported by NIMH grant R01 MH072672 and by a NIH Jointly Sponsored NIH Predoctoral Training Program in the Neurosciences training grant T32 NS082145.

17. **Effects of preconceptional corticosterone and prenatal antidepressant treatment on stress, responsivity and hippocampal neurogenesis in the next (F2) generation**. Abdul-Rahman Suleiman1, Susanne Brummelte1. 1Department of Psychology, Wayne State University, Detroit, MI 48202. The study was designed to investigate the effects of preconceptional maternal depression and gestational antidepressant treatment on the second generation. High levels of the stress hormone corticosterone (40 mg/kg) were given to female rats for 21 days before pregnancy to induce depressive-like behavior. Corticosterone-treated or healthy female rats (F0 generation) received sertraline (a selective serotonin reuptake inhibitor; 20mg/kg) or vehicle via oral gavage ~5 days prior to mating and continued the treatment until end of gestation. Female F1 offspring were mated with naïve males to produce the F2 generation. Adolescent male and female F2 rats were tested in several behavioral tests before being sacrificed and the brains extracted and processed for doublecortin (DCX) staining for immature neurons. Results suggest transgenerational effect of corticosterone exposure on the F2 litter weights but no strong effect on the adult behavioral outcome in the Forced Swim Test for depressive-like behavior or the Open Field Test for anxiety-like behavior. We hypothesize to see altered stress responses to the Restraint Stress Test in F2 offspring from F0 dams that received corticosterone and reduced levels of hippocampal neurogenesis. Our results will illuminate the potential transgenerational effects of maternal depression and antidepressant treatment for future generations.

18. **The effects of clomipramine on anxiety-related behavior and Dnmt3a mRNA expression in the mPFC of male and females rats**. Dana M. Smith, Chris Higham, Jaime Ransohoff, Christina M. Ragan. Department of Psychology and Neuroscience, Colgate University, Hamilton, NY. According to the National Institute of Mental Health, anxiety is the most prevalent mental disorder in the United States. Compared to men, women have nearly twice the lifetime rate of most anxiety disorders. Despite this prevalence, the etiology of anxiety disorders remains unclear. However, the wide use of selective serotonin reuptake inhibitors (SSRIs) and serotonin agonists in treatment of anxiety disorders suggests that serotonin plays a role. Additionally, men and women show different responsivity and tolerability to treatment. Evidence suggests women respond better to SSRIs and have a higher dropout rate when treated with tricyclic antidepressants, whereas men display the opposite trend. Here, we investigate the effects of the tricyclic antidepressant clomipramine on anxiety-related behavior and physiology in male and female rats. Baseline anxiety was measured with the commonly-used elevated plus maze. After the initial behavioral test, subjects received a low dose of clomipramine (5 mg/kg), a high dose of clomipramine (15 mg/kg), or a saline control for one day (acute), 7 days (short-term), or 21 days (chronic). Following treatment, we observed anxiety-related behavior in the light-dark box. Lastly, animals were sacrificed, their brains dissected, and qPCR was performed on medial prefrontal cortex (mPFC) tissue, which is a brain region associated with emotion regulation and anxiety. Males given a chronic low dose of clomipramine were significantly more anxious than females in the same condition, which did not support our initial prediction. Regardless of sex, chronic high clomipramine groups were more anxious than any other clomipramine group. While there were no differences in anxiety behavior among acute treatment groups, chronic high dose clomipramine females were significantly more anxious than chronic low clomipramine females. We are currently investigating the effect of short-term treatment on anxiety. Additionally, we are currently examining the expression of anxiety-associated DNA methyltransferase 3a (Dnmt3a) mRNA in the mPFC. It has been shown in adult mice that inducing anxiety leads to downregulated Dnmt3a, whereas overexpressing the gene reduces anxiety. Therefore, we are interested in studying Dnmt3a and its relationship with sex and treatment. Overall, this study provides valuable insight into the roles of sex, Dnmt3a expression, and SSRIs in anxiety treatment.

19. **Sexual behavior and pair bonding does not increase the number of new cells in the female and male prairie vole (Michrotus ochrogaster).** Aguilar TE1, Diaz NF2, Young LJ3, Paredes RG1 and Portillo W1. 1 Instituto de Neurobiologia, UNAM. Mexico, 2Instituto Nacional de Perinatologia, Isidro Espinosa de los Reyes. Mexico and 3Emory University, Atlanta Georgia. USA. Pair bonding is a hallmark of social monogamy that is displayed by prairie voles (*Michrotus ochrogaster*) after 6 hrs of cohabitation with mating. Previous studies in rats and mice have shown that mating induces neurogenesis in olfactory bulb (OB) and dentate gyrus of hippocampus (DG). This effect has been demonstrated in the amygdala (AMG) and ventromedial hypothalamus (VMH) in (gonadally intact) female prairie vole following exposure to unfamiliar male. The current study further explores whether cohabitation with mating for 6 hrs induces neurogenesis. Forty eight voles (24 males and 24 females) were randomly assigned into three groups: controls, social exposure and social cohabitation with mating. All females were ovariectomized and supplemented with estradiol during four days to induce sexual receptivity, males remained gonadal intact. In this paradigm, DNA synthesis marker 5-bromo-2- deoxyuridine (BrdU) was administrated 3 times every 2 hours to each group. Controls were isolated in different cages, while social exposure group remained in the same cage with a physical barrier, allowing odor

and visual stimuli between female and male. The social cohabitation with mating group was recorded during 24 hours and the parameters of sexual behavior were determined. Fifteen days later voles were perfused and brain tissue was collected. Brain sections were processed for BrdU immunostaining. No differences in the number of new cells (BrdU+) were found in the AMG, VMH, granular and glomerular layer of the accessory and main OB and the medial preoptic area (PMA) between the groups in males and females. These results do not support a role for neurogenesis in pair bonding. This research was supported by grants CONACYT 252756, 167101; Fronteras 374; UNAM-DGAPA-PAPIIT IN203615, IN210215; Instituto Nacional de Perinatologia 212250-3230-21216-05-15 and Red Temática Células Troncales y Medicina Regenerativa. We thank Francisco Camacho, Deisy Gasca and Carlos Lozano for their technical assistance.

20. **Neuroeconomics of Motherhood: Investigating the neurobiological effects of restricted resources and threat presence in lactating maternal rats (Rattus norvegicus).** Scarola, S1., Kent, M1., Bardi, M1., Neal, S1., Perdomo-Trejo, J1., Thompson, B., Lambert, S2., Lambert, K3. 1Randolph-Macon College, 2Furman University, 3University of Richmond. Maternal behavior is essential for both the continuation of mammalian species and the development of viable offspring. Thus, if maternal responses are disrupted due to various threatening factors, the costs are considerable. Consequently, it is important to understand the impact of various threats to adaptive and optimal maternal responses. Stress, for example, negatively impacts maternal responsiveness (Larson, 2007). In humans, a common stressor for mothers is derived from low socioeconomic status (SES) resulting in diminished necessary resources for raising a healthy family (Hackman et al., 2011). Accordingly, in the current study, a rodent model of varying SES levels was developed to investigate the effect of limited resources and unpredictable threats on maternal responsiveness. By assigning Long-Evans rats to treatment groups simulating low and high SES environments (i.e., altered levels of nesting material and bedding), maternal responsiveness (i.e., pup licking, pup huddling, nesting, nursing, pup retrieval, and pup retrieval across a novel barrier), as well as pup development (i.e., body weight, milk band size, and tail length), were assessed. More specifically, pregnant females were assigned to the following treatments during their lactation period: high SES, without the presence of an environmental threat (i.e., predator stimuli; n=7); high SES plus threat (n=8); low SES, without threat (n=7); and low SES plus threat (n=6). These conditions continued until the pups were weaned. On postnatal days 2 and 6, uninterrupted home-cage maternal behavior (i.e., pup licking, pup huddling, nest quality, and nursing) was observed for 5minutes. Results indicated that low SES interrupted maternal responsiveness and pup development; Specifically, compared to low SES maternal rats, high SES maternal groups had a significantly higher nest quality score ($p=0.001$), pup huddling score ($p=0.018$), and overall maternal index score ($p=0.018$; defined as all individual maternal behavior scores summed together). Additionally, focusing on pup development measures, high SES pups had significantly longer tails than low SES pups ($p=0.002$). Subsequently on post-natal days 2 and 6, maternal retrieval was assessed by dispersing three pups in the corners of a novel cage. Eight days following parturition, rats were exposed to a maternal challenge task in which a novel barrier had to be crossed to retrieve pups. The high SES groups exhibited a significantly faster total pup retrieval time in the maternal retrieval task ($p=0.051$); however, the threat groups had a significantly faster total pup retrieval time across the novel barrier ($p=0.05$). Further, baseline and post-behavioral test fecal samples were collected for stress hormone assays (i.e., corticosterone and DHEA) and brains were harvested at the end of the study for the assessment of neural markers of resilience (i.e., BDNF-

immunoreactivity in the hippocampus and NPY- immunoreactivity in the ARC and PVN). Endocrinological results indicated that high SES mothers had significantly higher DHEA (p=0.008) levels and DHEA/CORT ratio levels (p=0.0005; both measures of emotional resilience). Focusing on neural measures, compared to the high SES groups, lower levels of BDNF-immunoreactivity was observed in the hippocampus CA3 in low SES groups (p=0.001). Additionally, initial analyses suggest a trend of higher NPY-immunoreactivity in the PVN and ARC of high SES mothers, although the tissue is still being quantified. Thus, the results indicated compromised maternal responsiveness in low SES maternal groups, accompanied by heightened vigilance in the threat groups. Further, the neurobiological findings indicated compromised resilience in the low SES groups (evidenced by lower DHEA/CORT ratio and decreased BDNF-immunoreactivity levels). Taken together, exposure to restricted resources in the current study resulted in compromised maternal responsiveness. Considering that more than 16 million children were born into families below the poverty level in the United States in the year of 2016 (Child Poverty, 2016), this area deserves further research to understand threats to the well-being of both mothers and offspring. I express great gratitude to the Randolph-Macon College Schapiro Undergraduate Research Fellowship for the funding that made this research project possible.

21. **Central amygdala relaxin-3/rxfp3 signalling modulates alcohol-seeking in rats**. Leigh C Walker1,2, Hanna E Kastman1,2, Elena Krstew1,2, Andrew L Gundlach1,2 & Andrew J Lawrence1,2. 1 The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria 3052, Australia. 2 Florey Department of Neuroscience and Mental Health, The University of Melbourne, Victoria 3010, Australia. Alcohol use disorders are a leading cause of preventable deaths worldwide and stress is a major cause of relapse. The relaxin-3/RXFP3 system modulates stress-induced relapse to alcohol seeking in rats and while the bed nucleus of the stria terminalis has been implicated in this regard, the central nucleus of the amygdala (CeA) also receives a relaxin-3 innervation and CeA neurons densely express RXFP3 mRNA. Moreover, the CeA is consistently implicated in both stress and addictive disorders. Yohimbine precipitates relapse-like behaviour in rodents, although exactly how yohimbine induces relapse is unknown, possibly by increasing stress levels and inducing a heightened cue reactivity. Since alcohol use causes neuroadaptations in brain stress circuits, in the current study, we examined the effects of yohimbine (1 mg/kg, i.p.) on anxiety-like behaviour in alcohol-experienced rats. Further, we assessed CeA neuronal activation following yohimbine-induced reinstatement of alcohol seeking, and the role of the relaxin-3/RXFP3 signalling within the CeA in yohimbine-induced reinstatement to alcohol seeking. Low dose yohimbine was anxiogenic in rats with a history of alcohol use. Furthermore, home-cage yohimbine treatment and yohimbine-induced reinstatement of alcohol seeking both increased Fos activation in CeA GABAergic neurons compared to naïve and vehicle controls. Bilateral intra-CeA injections of the selective RXFP3 antagonist, R3(B1-22)R, attenuated yohimbine-induced reinstatement of alcohol seeking. Collectively, these data suggest the CeA is a node where yohimbine acts to induce reinstatement of alcohol seeking and implicates the relaxin-3/RXFP3 system within the CeA in this process.

22. **Time-restricted feeding exerts anti-inflammatory and neuroprotective effects on acute seizure model.** Santillan-Cigales, Juan Jair [1]; Landgrave-Gomez Jorge[1]; Mercado-Gomez Octavio Fabian[1]; Guevara-Guzman, Rosalinda[1]. [1]Universidad Nacional Autonoma de Mexico. During the past decade, experimental research has demonstrated a prominent role of the pro-inflammatory molecules on

epileptogenic and ictogenic processes. On the other hand, our research group recently demonstrated that time- restricted feeding (TRF) had an anticonvulsant effect, however, the precise mechanism by which this diet exerts its beneficial effects are still unknown. Our aim was to investigate whether TRF is able to exert its beneficial effect decreasing the expression of pro-inflammatory molecules and thus might have a neuroprotective role after seizure induction. Briefly, TRF consisted in allowing rats to eat for two hours daily during their light phase for 20 days; conversely, control group was fed *ad libitum* (AL). After dietary schedule, *status epilepticus* (SE) was induced using a pre-treatment with a injection of lithium chloride (3 mEq/kg) followed by pilocarpine administration (60 mg/kg).Both protein and mRNA expression of pro-inflammatory molecules such as interleukin 1 beta (IL-β), tumor necrosis factor alpha (TNF-á) and interleukin 6 (IL-6) were measured in hippocampus from each group 24 h after SE. Additionally, coronal brain slices were processed with fluoro-Jade C to mark degenerate neurons. Our preliminary data showed that the group that followed TRF before SE had a significant decrease in both of mRNA and protein expression of pro-inflammatory molecules (IL-β, TNF-á, IL-6), in comparison with AL group after seizure induction. Furthermore, the hippocampus from TRF group showed a significant decrease on reactive gliosis and less FluroJade-positive cells were observed after SE. Our data demonstrate that TRF may exert a neuroprotective effect by decreasing the mRNA and protein expression of pro-inflammatory molecules and reactive gliosis after seizure induction.

23. **Exploring Maternal-Based Neuroplasticity: Neuroanatomical modifications in the rodent prefrontal cortex**. Gibson, A.1, Kinsley, C.1, Kent, M.2, Lambert, K1. 1University of Richmond, 2Randolph-Macon College. Prior research indicates that motherhood and the hormones of pregnancy are associated with enhanced emotional regulation, spatial learning, and memory. These enhancements facilitate supportive maternal behaviors such as foraging and attentiveness to offspring. Observed behavioral changes in mothers provide a valuable foundation for the investigation of accompanying biological markers of neuroplasticity. Previous work has demonstrated a proliferation of hippocampal dendritic spines in females with reproductive experience compared to age-matched virgins, a finding that has been associated with the enhanced spatial learning observed in these animals. As part of a putative neuronal circuit, remodeling of the anterior cingulate cortex (ACC) may consolidate initially hippocampus-dependent memories for retrieval at later time points. Consequently, the present study investigated the ACC in female rats with varying levels of reproductive experience. Specifically, rats were assigned to nulliparous (n=6), 20-day pregnant (n=6) and 6-day lactating (n=6) groups. The brains were removed and prepared for Golgi-Cox histological assessment so that pyramidal-cell body areas and spine concentrations on the primary branch of the apical dendrite could be quantified. Results indicated that, compared to the nulliparous group, spine density was significantly elevated in the ACC of both late-pregnant ($p < 0.003$) and lactating ($p < 0.026$) rats without any observed differences in cell body area. These results corroborate past findings in the hippocampus and demonstrate that the neural modifications that accompany reproductive experience neural extends to cortical regions, likely facilitating the efficient behavioral and cognitive responses involved in the maternal rat's care for her offspring.

24. **A novel automated home-cage task to assess motor skill learning and fine motor control in a mouse model of Huntington's Disease.** Cameron L. Woodard1,2, Federico Bolaños1,2, James D. Boyd2, Timothy H. Murphy2, Lynn A. Raymond2. 1 Graduate Program in Neuroscience; 2 Department of Psychiatry and Djavad Mowafaghian Centre for Brain Health, University of British Columbia,

Vancouver BC Canada. Behavioral testing is a critical step in assessing the validity of rodent models of neurodegenerative disease, as well as evaluating the efficacy of pharmacological interventions. Recently, a number of automated systems have been developed to perform tracking and behavioral profiling of animals within their own home-cage, allowing for 24-hour monitoring and minimizing experimenter interaction. However as of yet, none of these systems have had functionality for the assessment of motor skill learning and fine motor control, which are highly relevant behaviours for movement disorders such as Huntington's and Parkinson's disease. To address this, we have adapted a novel paradigm that incorporates a lever-pulling task for water into the mouse home-cage. An automated system allows for continuous data collection over long periods (several weeks), and group-housed mice can be individually assessed via RFID tagging. Animals first learn a simple version of the task, before being moved to a second phase where they must hold the lever in a specified range of motion. Testing with this paradigm has revealed the presence of several distinct phenotypes in the YAC128 mouse model of Huntington's disease at 2 months (pre-symptomatic), 4-months (early symptomatic) and 6-months (symptomatic) of age. Pre-symptomatic, but not older, YAC128 mice display a decreased ability to adapt to changes in task demands when shifting to a more difficult task. In contrast, 4- and 6-month-old YAC128 mice exhibited circadian abnormalities and alterations on several kinematic measures, suggesting an impairment in motor control and persistence. As this system incorporates automated monitoring and minimal investigator interaction, we believe it has strong potential as a tool for the high-throughput identification of behavioral phenotypes in disease models. Support: Canadian Institutes of Health Research.

25. **Galanin-3 receptor antagonism by SNAP 37889 blocks cue-induced reinstatement of alcohol seeking in IP rats and increases c-Fos expression in the nucleus accumbens shell**. Kira-Elise Wilson1, Sigrid Limburg1, Melissa Duggan1, Adam J. Lawther1, Spencer J. Williams2, Andrew J. Lawrence3, Matthew W. Hale1†, Elvan Djouma4†. 1School of Psychology and Public Health, La Trobe University, Melbourne, Australia, 3086; 2Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Australia; 3Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia; 4School of Life Sciences, La Trobe University, Melbourne, Australia, 3086. Worldwide, 3.3 million people die each year due to the harmful use of alcohol, and 5.1% of the global burden of disease and injury is attributable to alcohol. The galanin-3 receptor subtype (GALR3) has been implicated in modulating the consumption of alcohol. We have previously shown that administration of the GALR3 antagonist SNAP 37889 decreases ethanol consumption in a fixed-ratio operant-responding paradigm, and attenuates cue-induced reinstatement. The current study employed an operant reinstatement paradigm to investigate the effects of SNAP 37889 on cue-induced reinstatement and c-Fos expression in the brains of alcohol-preferring (iP) rats. Eighteen iP rats were trained to self-administer 10% ethanol via a lever press, in the presence of visual and olfactory response-contingent cues. After 27 days of normal responding, response-contingent cues were then removed, leading to the extinction of lever-pressing behaviour. On the test day, rats were either treated with SNAP 37889 (30 mg/kg, i.p.) or vehicle (1ml/kg), before being exposed to operant chamber with the reinstatement of the visual and olfactory cues. Administration of SNAP 37889 reduced cue-induced reinstatement of ethanol-seeking behaviour. To examine the effect of GALR3 antagonism and cue-induced reinstatement on neuronal activation, c-Fos expression was measured in subregions of the medial prefrontal cortex (mPFC) and nucleus accumbens. Administration of SNAP 37889 increased c-Fos immunoreactivity in the nucleus accumbens shell, but was without effect in

the nucleus accumbens core region or the prelimbic and infralimbic regions of the mPFC. Additionally, the colocalisation of c-Fos protein expression within putative dopaminergic neurons in the caudal ventral tegmental area (VTA) was studied using c-Fos/tyrosine hydroxylase dual-label immunohistochemistry. An independent-samples t-test revealed no differences in c-Fos expression in dopaminergic and non-dopaminergic cells in the caudal VTA, between SNAP 37889 and vehicle-treated rats. Results from the current study support previous findings of GALR3 involvement in cue-induced reinstatement of alcohol-seeking behaviour, and provide novel evidence that GALR3 antagonism induces heightened neuronal activity in the nucleus accumbens shell. These data further highlight the potential therapeutic utility of GALR3 antagonism for preventing relapse in alcoholism.

26. **Left-right hemispheric functional asymmetry of ventral hippocampus and dorsolateral striatum**. Yukitoshi Sakaguchi1, Yoshio Sakurai1. 1Laboratory of Neural Information, Graduate School of Brain Science, Doshisha University, Japan. Functional asymmetry of brain hemispheres is a well-known feature in human, e.g., the left-sided function of language and the right-sided function of spacial cognition. However, such asymmetrical function is specific not only for human but also for various other animals. Some animals have right hemispheric dominance for dealing with anxiety, fear and stress responses and left hemispheric dominance for the formation of habits. Regarding the former lateralization, we performed anxiety-like behavioral experiment with “Successive alleys test”. The electrical lesion of the right ventral hippocampus (VH) led more increased entries to and times in the tip area of the alley than the lesion of the left VH. The immunohistochemical method with c-fos expression revealed more excitation of the right hemispheric VH in the alley. This result suggests that VH is related to anxiety, as the amygdala and medial prefrontal cortex are, and it has the right-sided functional asymmetry. Regarding the latter lateralization, we performed behavioral experiments with “Place/responce test” and “Devaluation test”. The excitotoxic lesion of the left dorsolateral striatum (DLS) led more attenuated habitual behaviors in both tests than the lesion of the right DLS. This result suggests the left-sided function of the DLS in habitual behaviors.

27. **Epigenetic involvement of the endocannabinoid vs. endovanilloid system in anxiogenic-like effects of nicotine as a stressor.** Tamaki Hayase, MD, PhD. Department of Legal Medicine, Kyoto University, Kyoto 606-8501, Japan. The addictive use of nicotine (NC) is associated with stressor-like emotional effects such as anxiogenic effects, although there seems to be lack of consensus concerning the underlying mechanisms due to the complicated involvement of target neurotransmitter systems. In the elicitation of the NC-related emotional symptoms including anxiety, the fundamental involvement of epigenetic mechanisms such as histone acetylation has recently been reported (Hayase, 2016). Furthermore, among the interacting neurotransmitter systems implicated in the effects of stressors, the endocannabinoid (ECB) and endovanilloid (transient receptor potential vanilloid 1: TRPV1) systems are considered to contribute indispensably to anxiety. These systems are distributed in the key brain regions responsible for defensive behavioral responses to stressors or aversive stimuli, which include the periaqueductal gray, hippocampus and medial prefrontal cortex. These regions are also closely associated with the target neurotransmitter systems of NC (e.g. nicotinic cholinergic system). In the present study, the epigenetic involvement of histone acetylation induced by histone deacetylase (HDAC) inhibitors was investigated in anxiety-related behavioral alterations caused by NC and/or immobilization stress (IM). Moreover, based on the contributory roles of the ECB and TRPV1 systems, the interacting influence of ECB and TRPV1 ligands on the effects of HDAC inhibitors was

evaluated in order to examine epigenetic therapeutic interventions. Anxiety-like behaviors in the elevated plus-maze test, which were observed in mice treated with repeated (4 days) NC (subcutaneous 0.8 mg/kg) and/or IM (10 min), were blocked by the HDAC inhibitors sodium butyrate (SB) and valproic acid (VA). The cannabinoid type 1 (CB1) agonist ACPA (arachidonylcyclopropylamide; AC) and the TRPV1 antagonist capsazepine (CZ) also antagonized the anxiogenic-like effects of NC and/or IM. Conversely, the anxiolytic-like effects of the HDAC inhibitors (SB and VA), like those of AC, were prevented by SR 141716A (SR). However, by combining CZ with SR, antagonistic effects of SR against the HDAC inhibitors or AC were counteracted. From these results, the opposing influence of ECB and TRPV1 systems on the NC and/or IM-induced anxiogenic-like effects was shown. Moreover, the combined involvement of HDAC inhibitor-induced histone acetylation vs. ECB and TRPV1 systems in anxiety-related behaviors was suggested.

28. **Involvement of the rat hippocampal NMDA and AMPA receptors in temporal order memory in radial maze.** Manami Sugita1, Kazuo Yamada1, Yukio Ichitani1. 1Faculty of Human Sciences, University of Tsukuba. Temporal order memory (TOM) is the memory for the order of past events. It has been reported that the hippocampal lesions in rats impaired TOM using radial maze. However, there are few previous studies that investigated the involvement of hippocampal neurotransmitter receptors in it. Here, we investigated the involvement of dorsal hippocampal N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in rats' TOM using radial maze. One trial of the task consisted of a study and a test phases. In the study phase, five arms were opened sequentially and the rat received a food reward at the end of each arm. The used arms in each trial and the order of arm presentation were at random. In the test phase, two arms that were presented second and forth in the study phase were opened simultaneously. Only the choice of the arm presented earlier in the study phase was rewarded. After animals reached the criterion, the drug test started. An NMDA receptor antagonist AP5 (20 or 40 mM), an AMPA receptor antagonist NBQX (5 mM) or vehicle (PB) was bilaterally injected into the dorsal hippocampus (1.0 µl/side) 10 min before the study phase. Both AP5 and NBQX injections disrupted performance of the task, suggesting that the dorsal hippocampal NMDA and AMPA receptors play an important role in rats' TOM in radial maze. However, since the radial maze was used in the current study to measure TOM, there was a possibility that the impairment observed might come from spatial memory deficit caused by the drug treatments. Therefore, we next investigated the effect of hippocampal NMDA and AMPA receptor blockade on rats' performance in the task that does not require TOM component. Thus, in the study phase, the procedure was the same as in the previous experiment. However, in the test phase, two arms were opened simultaneously, one was the familiar arm presented in the study phase and the other was the novel arm that the rat had not entered. The correct choice was defined as entering the novel arm. The drug test was conducted in the same way as the TOM task. From these two experiments, we will discuss the role of the hippocampal NMDA and AMPA receptors in rats' TOM in radial maze.

29. **Multiple functional significance of the glucose-monitoring neuronal network in the medial orbitofrontal cortex**. Istvan Szabo1, Edina Hormay1, Bettina Csetenyi1, Zoltan Karadi1,2. 1Institute of Physiology, Medical School, University of Pecs, Pecs, Hungary, 2Molecular Neuroendocrinology and Neurophysiology Research Group, Szentagothai Research Center, University of Pecs, Pecs, Hungary. The medial orbitofrontal cortex (mOFC) is known to play important roles in the central regulation of

feeding and metabolism. Since previous studies demonstrated the importance of glucose-monitoring (GM) neurons in these processes, our main goal was to characterize the multiple functional significance of these chemosensory cells. In our study, complex functional attributes of GM neurons were examined in the mOFC by means of electrophysiological, behavioral and metabolic investigations. In the electrophysiological experiments, single neuron responsiveness was recorded to microelectrophoretic and intraoral chemical stimulations on rats. One fifth of the mOFC neurons proved to be the element of the forebrain GM neural network. The GM and glucose-insensitive cells displayed differential catecholamine, as well as acetylcholine and GABA sensitivities. Gustatory stimulations with the primary taste qualities and orange juice elicited characteristic neuronal activity changes. After the selective destruction of GM cells by streptozotocin (STZ) behavioral and metabolic experiments were performed on rats. In the acute GTT, 30 and 60 minutes after the glucose load the blood glucose level in the STZ-treated rats was significantly higher than in the control animals. In the measurement of plasma concentrations of metabolites, the triglyceride level was significantly higher in the STZ-treated animals than in the control rats. No difference was found between the STZ-treated and control groups in the ability to acquire CTA. In taste reactivity test, individual pleasant and unpleasant score values did not differ significantly in the STZ-treated and control groups, nevertheless the STZ microinjected animals apparently felt both pleasant and unpleasant tastes more pleasant compared to the control rats. Our data indicate that GM neurons of the mOFC are of distinguished significance in the integration of signals arising from the internal and external environments to maintain the healthy homeostatic balance. Supported by: Ajinomoto 51064/2009; PTE AOK KA 2013/34039/1; EFOP-3.6.1-16-2016-00004.

30. **Bidirectional modulation of CB1 receptors influences compulsive-like and social interaction behaviors in a non-induced compulsive-like mouse model**. Marth, Tandi E.1,2; Mitra, Swarup1,2; Santana-Miranda, Vanessa3; Ghosh Basu, Debarati4; Poe, Brooks5; Mucha, Mackenzie6; Bult-Ito, Abel1,2. 1,2,3,4,5,6University of Alaska, Fairbanks. Not much research has been done to observe the effects of cannabinoids on obsessive-compulsive disorder (OCD). A unique animal model developed through bidirectional selection of the common house mouse (Mus musculus) has been shown to exhibit spontaneous compulsive-like behaviors and is used for this study. Here, we investigated compulsive-like and social interaction behaviors as a result of direct versus indirect modulation of the CB1 receptor in the compulsive-like mice. In compulsive-like nest-building behavior we found significant attenuation of nest-building among groups treated with the indirect CB1 receptor agonist URB597 in combination with the CB1 receptor antagonist SR171416A. This effect was also observed in mice treated individually with the CB1 receptor direct agonist WIN55,212-2. This effect was however not observed in compulsive-like marble burying behavior. These results indicate that direct activation of CB1 receptor by WIN55,212-2 can be anti-compulsive for specific compulsive-like phenotypes. The data from this research also indicates that agonist/antagonist combination treatment of URB597 + SR171416, also reduce the compulsivity of the mice in the nest-building activity probably due to other receptors involved. Funding was provided by an NIH program called the Biomedical Learning and Student Training program (BLaST), which is an undergraduate scholarship program offered at the University of Alaska, Fairbanks.

31. **The blockage of ventromedial hypothalamus CRF type 2 receptors impairs escape responses in the elevated T-maze**. Viana MB1, Silva MSCF1, Souza TMO1, Pereira BA1, Céspedes IC1, Bittencourt JC2.

1Departamento de Biociências, Universidade Federal de São Paulo, 11060-001, Santos, Brazil. 2Departamento de Anatomia, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 05508-000, Brazil. In a previous study, the administration of corticotrophin-releasing factor (CRF) into the dorsomedial hypothalamus (DMH), a region that modulates defensive reactions, was shown to facilitate elevated T-maze (ETM) avoidance responses, an anxiogenic-like effect. Intra-DMH administration of the CRF type 1 receptor (CRFR1) antagonist antalarmin induced anxiolytic-like effects and counteracted the anxiogenic effects of CRF. The present study further investigates the role played by CRF receptors of the medial hypothalamus in anxiety. For that, male wistar rats were treated with CRFR1 and CRFR2-modulating drugs in the DMH or VMH, another hypothalamic nucleus implicated with the defense and emotional behavior, and tested in the ETM for inhibitory avoidance and escape measurements. In clinical terms, these responses have been respectively related to generalized anxiety and panic disorder. All animals were tested in an open field, immediately after the ETM, for locomotor activity assessment. The results showed that intra-VMH CRF or antalarmin did not alter ETM avoidance or escape performance. Intra-VMH injection of the CRFR2 preferential antagonist antisauvagine-30 or of the selective CRFR2 antagonist astressin 2-B inhibited escape performance, a panicolytic-like effect, without altering avoidance reactions. The CRFR2 agonist urocortin-2 intra-VMH was by itself without effect but blocked the effects of astressin 2-B. None of the drugs administered into the DMH altered ETM measurements. Additionally, none of the compounds altered locomotor activity measurements. These results suggest that VMH CRFR2 modulate a defensive response associated with panic disorder and are of relevance to the better understanding of the neural mechanisms underlying this pathological condition. Funding: FAPESP, CNPq (Brazil).

32. **A non-invasive eye tracking study using rhesus macaques and titi monkeys.** Takeshi Murai1,2, Sara M. Freeman1, Michelle C. Palumbo1, Casey Phi1, Karen L. Bales1,3 and Melissa D. Bauman1,4,5. 1California National Primate Research Center, University of California-Davis, Davis, CA USA 95616. 2Biomarker Group, Drug Development Research Laboratories, Sumitomo Dainippon Pharma Co., Ltd., Osaka, Japan. 3 Department of Psychology, University of California-Davis, Davis, CA USA 95616. 4Department of Psychiatry and Behavioral Sciences, University of California-Davis, Sacramento, CA USA 95817. 5The MIND Institute, University of California-Davis, Sacramento, CA USA 95817. Visual information is one of the most important cues in social cognition for both humans and non-human primates. Individuals diagnosed with neurodevelopmental or neuropsychiatric disorders, such as autism or schizophrenia, display aberrant gaze patterns toward social stimuli. Developing minimally invasive eye-tracking protocols for use in nonhuman primates would provide useful tools to investigate biology and drug effects on gaze patterns. In this study, we established a novel non-invasive eye tracking method using Tobii Pro (TX300). Modified transfer boxes were used as the testing environment. The front panel of the boxes had a viewing window at approximately eye level. Subjects could move freely in the boxes and the window helped to direct gaze towards the display. Six infant (one male and five females) and four juvenile (two males and two females) rhesus macaques were presented still images (facial expressions) and videos (mother-infant interaction) of other rhesus monkeys in each session. Each monkey performed six eye tracking sessions within 60 days with a minimum 3-day interval between sessions. Rhesus monkeys preferred looking at video stimuli compared to still images ($p<0.01$). There were no differences in the looking time between infants and juveniles on the first session. However, juveniles looked at the stimuli, especially the videos, more

than infants in the later sessions. The method was also applied to monogamous coppery titi monkeys (Callicebus cupreus, eight juveniles and eleven adults). Like rhesus monkeys, titi monkeys spent a significantly longer time looking at videos compared to still images ($p<0.02$). Juveniles spent significantly more time looking at the stimuli than adults ($p<0.03$). It is noteworthy that none of the animals were trained or habituated prior to testing. This method will contribute to a better understanding of monkeys' visual processing of social cognition and development of novel treatments for neurodevelopmental and neuropsychiatric disorders. This study is funded by R21HD080498, OD011107, HD071998 and the Good Nature Institute.

33. **Reduced memory and recognition in prenatal valproic acid-exposed mice model of autism spectrum disorder influence the offspring's function of memory.** Misato, Yoshikawa; Hiroaki, Aso; Masahiko, Watanabe; Katsuya, Suemaru. Department of Public Health, School of Pharmacy, Shujitsu University. Autism spectrum disorder (ASD) is a pervasive developmental disorder characterized by two core behavioral symptoms of social deficits and stereotyped/repetitive behaviors. Both genetic and environmental factors are involved in the pathogenesis of ASD. Environmental factors include prenatal exposure to drugs, such as valpronic acid (VPA) which is an antiepileptic drug and histone deacetylase (HDAC) inhibitor. HDAC inhibition causes the changes in gene expression of ASD-related molecules. VPA-exposed mice have been used as model of ASD. In this study, we investigated whether behavioral deficits in VPA-exposed ASD mice are transmitted to the next generation (F1). VPA was administered intraperitoneally to the pregnant mice at 300 mg/kg dosage on embryonic day 10 (E10) and 400 mg/kg on E12. The male offspring (F0) have showed impaired sociability and preference for social novelty in the three-chambered social test and spatial memory in Morris water maze test. But the female offspring have showed impaired spatial memory only. Next we obtained F1 mice by crossing between male and female offspring from VPA-treated mother mice and investigated F1 mice's behaviors for sociability and memory/recognition. Sociability of F1 male mice was normal, but not preference for social novelty. F1 male mice decreased the function of spatial memory in Morris water maze test and object recognition memory in novel object recognition test. In conclusion, sociability deficit in the offspring from VPA-treated mother mice wasn't transmitted to F1 mice. But F1 mice showed reduced social, spatial, and object recognition memory, indicating perirhinal cortex and hippocampus related memory impairments. These results suggest that prenatal exposure to VPA affects changes in gene expression in the memory and recognition related brain area as an epigenetic change.

34. **Sex differences and modulation by sex hormones of risk-based decision making with acute administration of amphetamine**. Shunya Yagi1, Steven R. Wainwright1, Stephanie E. Lieblich2, Stan B. Floresco2, Liisa A. M. Galea1,2,3. Graduate Program in Neuroscience1, Department of Psychology2, Centre for Brain Health3, University of British Columbia.Vancouver Canada. Dopaminergic neurotransmission within the mesocorticolimbic pathway is known to alter risk-based decision making in rodents. Testosterone and estradiol levels have been shown to modulate reward related neural function and risk-taking behaviours in both men and women respectively and the gonadal hormones are known to modulate dopaminergic tone and axon density within the nucleus accumbens and medial prefrontal cortex. The objectives of this study were to determine the effect of estradiol and testosterone on rodent performance within a probabilistic discounting task. Male and female Long-Evans rats were either bilaterally gonadectomized (GDX) or received sham-operation (Sham) All

rats received single injections of vehicle, testosterone proprionate (0.2mg;1mg) or estradiol benzoate (0.3µg). After completion of hormone treatments we assessed the effects of amphetamine (0.125mg/kg;0.5mg/kg) on risk-based decision making. Rats were tested in a probabilistic discounting task in the operant chamber consisting of two levers; one the Large/Risky lever, the other the Small/Certain lever. Rats received daily sessions 6-7 days per week, consisting of 4 blocks of 18 trials that were comprised of 8 forced-choice trials where only one lever was presented (4 trials for each lever, randomized in pairs) permitting animals to learn the amount of food associated with each lever press and the respective probability of receiving reinforcement over each block. This was followed by 10 free-choice trials, where both levers were presented and the animal chose either the Small/Certain or the Large/Risky lever. Choice of the Small/Certain lever always delivered one pellet with 100% probability; choice of the Large/Risky lever delivered 4 pellets but with a particular probability. The probability of obtaining 4 pellets after pressing the Large/Risky lever was initially 100%, then 50%, 25%, and 12.5%, respectively, for each successive block. Our results demonstrate that males showed significantly greater choice of the large/risky lever in both the 25% and 12.5% probability trial blocks compared to females. High, but not low, testosterone treatment reduced risky decision making in the 12.5% probability trial blocks in the castrated rats, while estradiol treatment did not influence risky decision making either in males or females. Furthermore, the high dose of amphetamine increased lever pressing in the 25% probability trial blocks in the Sham group, and in the 12.5% probability trial blocks in both the Sham and GDX groups in regardless of sex. These findings indicate that testosterone modulates male risk related behaviors and gonadal hormones facilitate the effects of amphetamine to increase risky decision making. NSERC grant 203596-13.

35. **Mice that lack zinc transporter 3 (ZnT3) do not exhibit generalized social avoidance following repeated social defeat stress**. Brendan McAllister, Richard Dyck. University of Calgary. Zinc transporting proteins are crucial for maintaining zinc homeostasis throughout the body. In the central nervous system, one such protein – zinc transporter 3 (ZnT3) – grants zinc an intriguing ability, allowing this essential element to act as a neurotransmitter. In forebrain regions including the hippocampus, amygdala, and neocortex, ZnT3 sequesters zinc ions within synaptic vesicles in a subset of the glutamatergic neurons. This “vesicular zinc” can then be released into the synaptic cleft in an activity-dependent fashion, where it exerts signaling functions through a plethora of targets. Previous research has examined the functional significance of vesicular zinc by studying ZnT3 knockout (KO) mice, which completely lack vesicular zinc storage and release. In general, these mice perform normally in standard behavioural tests, but abnormalities are unmasked when the mice are challenged by advanced age or with more difficult testing. Additionally, ZnT3 KO mice are deficient in some forms of experience-dependent plasticity. Here, we investigated how ZnT3 KO mice are affected by a different form of challenge that is associated with substantial plasticity in the brain: chronic stress. To induce stress, we used the repeated social defeat model, which is commonly used to characterize susceptibility to stress, and is well-established to induce anxiety- and depression-like behaviours. Male wild type and ZnT3 KO mice were subjected to ten episodes of social defeat by aggressive CD-1 mice over a 10 day period. This was followed by a battery of behavioural tests, which included tests of social interaction, anxiety, and cognition. We found that mice of both genotypes showed anxiety-like behaviour following stress, and both genotypes became socially avoidant of a CD-1 mouse. However, only wild type mice became avoidant of a novel conspecific; ZnT3 KO mice did not. By contrast, in a fear conditioning test, stress potentiated the cued fear memory of ZnT3 KO mice

but not wild type mice. Finally, 10 days of defeat stress did not impact cellular proliferation in the hippocampal dentate gyrus in either genotype. In summary, ZnT3 KO mice are abnormal in their response to chronic social defeat stress, though we could not establish a clear increase or decrease in stress susceptibility. The interaction between chronic stress and ZnT3 status instead seems to differ across behavioural domains. Funding provided by NSERC and the Killam Trusts.

36. **Timing and amounts of high fat diet intake affect the benefit which improves social avoidance induced by social defeat stress.** Airi Otsuka1, 2, Tetsuya Shiuchi1, Hiroyoshi Sei1. 1Department of Integrative Physiology, Institute of Health Biosciences, Tokushima University Graduate School, 2Research Ferrow of Japan Societybfor the Promotion of Science. Exposure to a psycho-social stress is one of risk factor for depression. Social-defeat stress (SDS) model is a well-known paradigm for human's psycho-social stress model. Rodents exposed to SDS show a variety of behavioral changes, including depressive-like behavior and social avoidance. On the other hand, chronic stress affects food preference. Human exposed chronic life stress instinctively or emotionally seek out and consume energy dense food (comfortable food). Thus, eating comfortable food has possibility to improve stress induced behavior. However the comfortable food often causes obesity. In this study, first, we determined whether restricted high-fat diet (HF) which did not affect body weight was able to improve social avoidance induced by SDS. We used HF as a comfortable food. Male C57BL/6 mice were attacked by retired ICR mice for 2.5 min every day. One group was given HF restricted for 2 hours after attacked (HFR); another group was given HF ad libitum (HFA). Ten days later, we performed behavioral tests for both of studies to assess the SDS effect on anxiety behavior, depressive like behavior, and social activity. SDS-exposed mice showed social avoidance, compared with non-stressed control mice, both of which were given normal diet (ND). SDS-exposed HFA group improved this negative social behavior with increase of body weight whereas HFR showed similar improvement of social interaction without change of body weight. Next, we investigated whether timing and amounts of HF intake were involved in improvement of social behavior. Same mice were separated to HF restricted amount groups (50% and 25 % compared with SDS-exposed HFR group) or HF time shift groups (6 h and 12 h after SDS physical attack). And these groups bred previous schedule. HF restricted amount groups did not show HF benefit which improve social activity. Moreover HF restricted 25 % amount group showed anxiety behavior in open field test. HF time shift groups tended to improve social activity (not sufficient), and those group also showed decrease of total distance in social interaction test. Our results suggest that eating HF improve social activity induced by psycho-social stress, but it is important timing and amount of HF intake after stress exposure to reap that HF benefit.

37. **Cannabinoid type 2 receptors in brain dopamine neurons modulates anxiety-like and psychostimulant behaviors in floxed DAT-Cnr2 mouse model**. H. ISHIGURO1, 2, E. S. ONAIVI1, A. Canseco-Alba1, H. ZHANG3, E. L. GARDNER3, Z.-X. XI3, Q.-R. LIU1, 4. 1William Paterson University, Wayne, NJ, 2University of Yamanashi, Yamanashi, Japan, 3NIDA-IRP/NIH, Baltimore, MD, 4NIA-IRP/NIH, Baltimore, MD. The functional neuronal expression of CB2 cannabinoid receptors has been a subject of controversy and debate and had been referred to as a "sphinx" wrapped in a mystery with "identity crisis", but no more. This is because research activities from our lab and those of others have found and reported that CB2Rs are expressed in the mammalian brain and functionally involved in several dopamine (DA)-related and other CNS disorders including drug addiction in rodent models.

Therefore, manipulation of CB2R in mouse models is of critical importance in characterizing the molecular basis of CB2R neuronal signaling mechanisms. The two available CB2R gene knockout mice contain partial Cnr2 gene deletion at C- and N- terminal amino acid sequences and residues of CB2R activities might remain. Furthermore, these germline knockout mice in which the CB2R function could be compromised by developmental compensation are not suitable for tissue- and cell-type specific studies at molecular, pharmacological and behavioral levels. Therefore, we have generated Cnr2-floxed mice that were crossed with DAT-Cre mice, in which the Cre recombinase expression is under DAT (dopamine transporter) gene promoter control, to generate conditional CB2-KO mice in midbrain DA neurons in DAT-Cre-Cnr2-Lox transgenic mice. By using a novel highly-sensitive RNAscope in situ hybridization method, we detected clear CB2R mRNA expression in VTA DA neurons in Dat-heterozygous and wildtype control mice, but not in conditional CB2-KO mice, suggesting neuronal CB2R gene expression in VTA DA neurons. The performance of the conditional DAT-Cnr2 mutant mice were determined in motor function and emotionality tests in comparison to wild type controls. We report that in the motor function test using the spontaneous wheel running monitors, DAT-Cre-Cnr2 homozygous mice were more responsive to cocaine induced motor activity than heterozygous and wild type mice. In the plus maze test of aversive behavior, DAT-Cre-Cnr2 homozygous mice were less aversive to the open arms of the maze than the heterozygous and the wild type mice. We conclude that CB2R in dopaminergic neurons plays a role in modulating anxiety-like and psychostimulant motor behaviors in mice.

38. **Effect of oleuropein on cognitive deficits and changes in hippocampal BDNF and cytokine expression in a rat model of post-traumatic stress disorder**. Bombi Lee[1], Insop Shim[1,2], Hyejung Lee[2] And Dae-Hyun Hahm[1,2,]. [1]Acupuncture and Meridian Science Research Center, College of Korean Medicine, Kyung Hee University, Seoul, 02447, Republic of Korea. [2]The Graduate School of Basic Science of Korean Medicine, College of Korean Medicine, Kyung Hee University, Seoul, 02447, Republic of Korea. Post-traumatic stress disorder (PTSD) is a condition that develops after an individual has experienced a major trauma. This psychopathological response to traumatic stressors induces learning and memory deficits in rats. Oleuropein (OLE), a major compound in olive leaves, has been reported to possess several pharmacological properties, including anti-cancer, anti-diabetic and anti-atherosclerotic and neuroprotective activities. However, the cognitive effects of OLE and its mechanism of action have remained unclear in PTSD. In this study, we examined whether OLE improved spatial cognitive impairment induced in rats following single prolonged stress (SPS), an animal model of PTSD. Male rats were treated intraperitoneally (i.p.) with vehicle or various doses of OLE for 14 consecutive days after the SPS procedure. The SPS procedure resulted in cognitive impairment in the object recognition task (ORT) and the Morris water maze (MWM) test, which was reversed by OLE (100 mg/kg, i.p). Additionally, as assessed by immunohistochemistry and RT-PCR analysis, the administration of OLE significantly alleviated memory-associated decreases in the levels of brain-derived neurotrophic factor (BDNF) and cAMP-response element-binding protein (CREB) and mRNAs in the hippocampus. Together, these findings suggest that OLE attenuated SPS-induced cognitive impairment significantly by inhibiting the expression of pro-inflammatory mediators in the rat brain. Thus, OLE reversed several behavioral impairments triggered by the traumatic stress of SPS and is a potential non-invasive therapeutic intervention for PTSD (This research was supported by a Grant from the National Research Foundation of Korea funded by the Korean government (2016R1D1A1A09917012)).

39. **Effects of Ginsenoside Rb1 on rescues anxiety-like responses in a rat model of post-traumatic stress disorder**. BOMBI LEE1, INSOP SHIM1,2, HYEJUNG LEE2 AND DAE-HYUN HAHM1,2. 1Acupuncture and Meridian Science Research Center, College of Korean Medicine, Kyung Hee University, Seoul, 02447, Republic of Korea. 2The Graduate School of Basic Science of Korean Medicine, College of Korean Medicine, Kyung Hee University, Seoul, 02447, Republic of Korea. Single-prolonged stress (SPS), a rat model of post-traumatic stress disorder (PTSD), induces alterations in the hypothalamic-pituitary-adrenal axis. Korean red ginseng, whose major active component is ginsenoside Rb1 (GRb1) is one of the widely used traditional anxiolytics. However, the efficacy of GRb1 in alleviating PTSD-associated anxiety-like abnormalities has not been investigated. The present study used several behavioral tests to examine the effects of GRb1 on symptoms of anxiety in rats after SPS exposure and on the central noradrenergic system. Male Sprague Dawley rats received GRb1 (10 or 30 mg/kg, i.p., once daily) during 14 days of SPS. Daily GRb1 (30 mg/kg) administration significantly increased the number and duration of open arm visits in the elevated plus maze (EPM) test, reduced the anxiety index, increased the risk assessment, reduced grooming behaviors in the EPM test, and increased the total number of line crossings of an open field after SPS. The higher dose of GRb1 also blocked SPS-induced decreases in hypothalamic neuropeptide Y expression, increases in locus coeruleus tyrosine hydroxylase expression, and decreases in hippocampal mRNA expression of brain-derived neurotrophic factor. These findings suggest that GRb1 has anxiolytic-like effects on both behavioral and biochemical symptoms similar to those observed in patients with PTSD (This research was supported by a Grant from the National Research Foundation of Korea funded by the Korean government (2016R1D1A1A09917012)).

40. **Gastrodin ameliorates development of depression-related symptoms induced by single prolonged stress in rats**. BOMBI LEE1, INSOP SHIM1,2, HYEJUNG LEE2 AND DAE-HYUN HAHM1,2. 1Acupuncture and Meridian Science Research Center, College of Korean Medicine, Kyung Hee University, Seoul, 02447, Republic of Korea. 2The Graduate School of Basic Science of Korean Medicine, College of Korean Medicine, Kyung Hee University, Seoul, 02447, Republic of Korea. Exposure to severe stress can lead to the development of neuropsychiatric disorders such as depression and post-traumatic stress disorder (PTSD) in at-risk individuals. Gastrodin (GAS), a primary constituent of an Oriental herbal medicine, has been shown to effectively treat various mood disorders. Thus, the present study aimed to determine whether GAS would ameliorate stress-associated depression-like behaviors in a rat model of single prolonged stress (SPS)-induced PTSD. Following the SPS procedure, rats received intraperitoneal administration of GAS (20, 50, or 100 mg/kg) once daily for 2 weeks. Subsequently, the rats performed the forced swimming test, and norepinephrine (NE) levels in the hippocampus were measured. Daily GAS (100 mg/kg) significantly reversed depression-like behaviors and restored SPS-induced increases in hippocampal NE concentrations as well as tyrosine hydroxylase expression in the locus coeruleus. Furthermore, the administration of GAS attenuated SPS-induced decreases in the hypothalamic expression of neuropeptide Y and the hippocampal mRNA expression of brain-derived neurotrophic factor. These findings indicate that GAS possesses antidepressant effects in the PTSD and may be an effective herbal preparation for the treatment of PTSD (This research was supported by a Grant from the National Research Foundation of Korea funded by the Korean government (2016R1D1A1A09917012)).

41. **Disconnection between the insular cortex and amygdala accelerates binge-like sugar overconsumption in mice**. Yasunobu Yasoshima. Osaka University. Our previous study showed that daily limited access to a sucrose solution in food deprivation schedule gradually increased sucrose consumption in mice, resulting in binge-like overconsumption of the sugar. The study also implicated that the binge-like sucrose consumption was mediated by hedonic motivation to consume the palatable sweet tastant. However, it remains unsolved whether higher-order gustatory processing in the insular cortex plays a role in hedonic-driven sucrose overconsumption. To access the issue, we examined the effect of bilateral lesions of the insular cortex (IC) on the binge-like behavior. Bilateral lesions of the insular cortex, but not of the thalamic gustatory area, accelerated development of the binge-like overconsumption in food-deprived mice, suggesting that the cortical gustatory processing in the IC is not necessary to develop the binge-like sucrose overconsumption. Next, to investigate neural circuitry mechanisms for the acceleration, we focused on the reciprocal connections between the IC and the amygdala (AMY). The effect of disconnection between these brain sites in the same hemisphere was examined. Mice were divided into the following three groups: asymmetric lesions, symmetric lesions and sham-lesioned control groups. Both of asymmetric and symmetric groups received a unilateral lesion of the IC. The asymmetric group received a unilateral lesion of the AMY in the contralateral side, resulting in disconnection between these brain areas in the both hemisphere. The symmetric lesions with unilateral lesions of the IC and AMY in the same hemisphere resulted in intact connection between the two areas in the contralateral side. Only the asymmetric group consumed significantly more sucrose than both symmetric lesions and sham-lesioned control groups in the limited access procedure. The present findings showed that disconnection between the IC and AMY accelerates binge-like sugar overconsumption, suggesting that intact communication between the IC and the AMY play a suppressive role in binge-like sucrose-taking behavior. Supported by grants from Asahi Beer Foundation.

42. **A functional polymorphism of the mu-opioid receptor gene is associated with psychological characteristics and left anterior insula volume in the Japanese population.** Yumiko Kubo1,2, Hikaru Takeuchi3, Yoshie Kikuchi2, Chiaki Ono2, Yoshiyuki Kasahara1,2, Zhiqian Yu1,2, Shuken Boku4, Akitoyo Hishimoto4, Ichiro Sora4, Yasuyuki Taki5, Ryuta Kawashima3,6, Hiroaki Tomita1,2. 1Dept. Disaster Psychiatry, Tohoku Univ. Grad. Sch. of Med., Sendai, Japan; 2Dept. Disaster Psychiatry, IRIDeS, Tohoku Univ., Sendai, Japan; 3Div. Developmental Cognitive Neuroscience, IDAC, Tohoku Univ., Sendai, Japan; 4Dept. Psychiatry, Kobe Univ. Grad. Sch. of Med., Kobe, Japan; 5Dept. Nuclear Medicine and Radiology, IDAC, Tohoku Univ., Sendai, Japan; 6SAIRC, IDAC, Tohoku Univ., Sendai, Japan. The mu-opioid receptor (MOR) is involved not only in physical pain but also in social pain, such as social exclusion. The single-nucleotide polymorphism (SNP) c.118A>G of MOR gene (OPRM1) has been shown to be associated with the expression level and functional potency of the MOR. The anterior cingulate cortex and the anterior insula have been demonstrated to play major roles in the emotional components of pain. Intriguingly, PET studies have indicated that the magnitude of the negative emotional response to experimentally administered social pain is correlated with the degree of MOR system deactivation in the anterior cingulate cortex and left insula. Furthermore, the OPRM1 c.118A>G SNP was shown to be involved in the neural response of the anterior cingulate cortex and left anterior insula to a negative social condition. Based on these findings, we hypothesized that there may be a genetic influence of the MOR on these brain structures, which could contribute to psychological characteristics, such as negative emotions and personality traits, underlying variabilities

in the pain sensitivity. We analyzed genetic influences of the OPRM1 c.118A>G SNP on negative emotions and personality traits as well as the related brain structures among 768 young adults from the Japanese population. Carriers of more G alleles showed significantly lower scores of trait anger and trait anxiety. Carriers of more G alleles also showed significantly lower neuroticism and significantly higher internal locus of control. G allele carriers had significantly higher gray and white matter volumes of the left anterior insula, while there was no significant difference in anterior cingulate cortex volume among the genotypic groups. These findings suggest that the OPRM1 c.118A>G SNP may influence psychological characteristics and brain structure. The association between the genetic variance of OPRM1 c.118A>G and negative emotions as well as left anterior insula volume can contribute to the mechanisms underlying the individual variability in the emotional components of pain.

43. **A cohort study on the predictability of the risk of mental health disorders using temporal information of handwriting**. Mashio Y1, Yoshizaki T2, Ota M2 and Kawaguchi H1. 1 Graduate School of Life Sciences, Toyo University. 2 Department of Nutrition, Toyo University. The number of patients with mental health disorders has been increasing recently. Our previous study suggested we may be able to predict the risk of mental health disorders by analyzing the temporal information of handwriting, using a digital pen that digitized handwriting with resolutions of 0.3 mm and 13 ms. The aim of this study was to confirm the predictability of the risk and establish a feasible coping strategy at an individual level in the high risk group. A total of 86 students (aged 18–22) were recruited for a follow-up cohort study conducted over three years from 2014 to 2016. The participants voluntarily completed the Uchida–Kraepelin test, the GHQ-30 mental health questionnaire, the DIHAL.2 life habit questionnaire, and the DHQ-L diet questionnaire. The participants were classified into two groups according to the extent their total score on the GHQ-30 had changed: the first group included participants with an increased total score on the GHQ-30 from year one to year three (that is, the disimproving group); the second group included participants demonstrating a decreased total score on the GHQ-30 from year one to year three (that is, the improving group). Participants with a stable total score on the GHQ-30 from year one to year three were excluded due to low numbers ($n = 8$). We analyzed the differences seen between the groups for each scale score and the nutrition ratio of the DIHAL.2 and DHQ-L questionnaire as of 2014, using t-tests and the Mann–Whitney U test. Significant differences were observed with respect to Social health, Exercise consciousness and Copper intake ratio in 2014 between the groups ($p < 0.05$). Multiple regression analysis (stepwise) was also used to evaluate the variables described above, and other variables relating to mental health, for any association with the variation in total score on the GHQ-30 from year one to year three. Analysis showed that variation in the total score on the GHQ-30 from 2014 to 2016 was negatively associated with Exercise consciousness and Copper intake ratio in 2014 ($\beta = -0.29$, $p < 0.01$ and $\beta = -0.24$, $p < 0.05$). Therefore, this study suggests that increasing Exercise consciousness and Copper intake could improve the state of mental health. The protocols used in this study were approved by the Ethics Committee at Toyo University. This work was supported by KAKENHI (No. 26350874).

44. **Varieties of Attentional Effort: Individual Differences in psychophysiology**. Samira Aminihajibashi[1], Thomas Hagen[1], Maja Dyhre Foldal[1], Jens Maruis Halvorsen[1], Bruno Laeng[1], Thomas Espeseth[1]. [1] Department of Psychology, University of Oslo, Oslo, Norway. It is known that individual differences in the attentional effort and the allocation of mental resources during attentional tasks can be indexed

by task-evoked pupillary changes. Additionally, animal and imaging studies have provided evidence that pupillary changes associate closely with activity in locus coeruleus noradrenergic system (LC-NE) of the brain. One question is whether baseline pupil size and task-evoked pupillary changes are related to individual differences in the general cognitive ability (i.e. IQ), or related to individuals' level of expertise in specific attentional domains (as reflected in task performance). If pupil size is related to the general cognitive capacity (IQ), then one may expect 1) significant difference in baseline pupil size between individuals with high and low working memory, 2) significant difference in task-evoked pupillary changes between individuals with high and low IQ, and 3) positive inter-correlations between task-evoked pupillary responses across different tasks. To investigate the above questions, healthy Norwegian participants were asked to perform a multiple object tracking task (MOT) and an AX- continues performance task (AX-CPT) while their pupil size was measured by an eye-tracker. MOT task measures individuals' ability in sustained and divided attention under different level of perceptual load. AX- CPT measures the ability to regulate attention and responses according to the context information (known as proactive control), or based on recent events (i.e. reactive control). Results replicate the effects of mental effort on pupillary dilations within each tasks, i.e. more difficult conditions induced larger pupil size. While in AX-CPT, the proactive subjects had faster reaction times and larger pupil size in all trials, in MOT, we found an interaction showing that subjects with high accuracy (i.e., MOT capacity) had a larger pupil size in high loads, but smaller pupil size in low loads. However, we did not find evidence for any of predictions mentioned above. Thus, our data do not indicate a significant effect of general cognitive abilities on pupil size. To the contrary, it seems that task-evoked pupillary changes are better related to individual differences in the level of expertise in each specific attentional domain, rather than general cognitive capacity. Alternatively, uncorrelated pupillary changes across the tasks can be due to the differences in the individuals' level of interest, stress, and mind wandering for the different tasks. Acknowledgments This work was funded by a grant from Norwegian Research Council.

45. **Bidirectional modulation of threat processing by reversible pharmacological manipulation of basolateral amygdala in macaques.** Ludise Malkova1,2, Catherine Elorette1,2, Celestino Castanon1, Patrick A. Forcelli1,2. 1Department of Pharmacology and Physiology and the 2Interdisciplinary Program in Neuroscience, Georgetown University Medical Center, Washington, DC 20007, USA. The amygdala is a crucial part of the circuitry critical for processing of threat and eliciting appropriate responses after threat detection. It is also involved in regulation and/or modulation of appetitive and social behaviors. Previously we found that reversible pharmacological inhibition of the basolateral amygdala (BLA) by bilateral intracerebral infusions of the GABAA agonist muscimol increased affiliative social interactions between monkeys that were highly familiar with each other while administration of systemic diazepam resulted in no effect. This indicated that BLA-inhibition effects on social interactions are likely independent of changes in fear or anxiety. We also found that BLA disinhibition by infusions of the GABAA antagonist bicuculline methiodide resulted in reduced interactions (Wellman et al., 2016). Here we investigated whether similar BLA manipulations would affect reactivity to emotional stimuli outside the social setting. Six juvenile male macaques were tested on a behavioral paradigm in which emotionally salient (social and nonsocial: taxidermic snakes, videos of staring monkeys or unfamiliar humans) and neutral stimuli (novel objects, naturalistic videos) were presented. The latency to retrieve a food reward placed either on top of a transparent box containing these objects or in front of a screen playing a brief videoclip was measured along with

the time spent looking at the stimulus. This task pits the animal's desire for food against its desire to avoid a potentially threatening stimulus. BLA inactivation significantly reduced the latency to retrieve the food reward in the presence of a snake compared to baseline ($p<0.05$). Repeated snake presentations resulted in habituation of the response, i.e. reduction in latency to retrieve reward. Subsequent BLA disinhibition by BMI significantly increased the latency compared to the most recent baseline. This manipulation reproduced and even exceeded the fear response observed under the original (unhabituated) baseline. These bidirectional effects support the idea that BLA is the critical mediator of emotional threat processing. This result complements previous finding showing decreased fear of snakes after lesions of the central nucleus of amygdala in macaques (Kalin et al., 2004). Responses to social stimuli varied, indicating that, consistent with our above-cited finding, the role of BLA in modulating social behavior is unrelated to its action in threat detection. Supported by R01 MH099505.

46. **Liposomes treatment antagonized dendritic spine loss and reduction of neurogenesis in hippocampus of chronically stressed rats**. Mostallino, Maria Cristina1; Biggio, Francesca2; Boi, Laura2; Locci Valentina2; Toffano3, Gino3; Biggio, Giovanni1,2. 1Institute of Neuroscience, National Reserach Council, CNR, Monserrato, Italy; 2Department. of Life and Environmental Sciences, section Neurosci., University. of Cagliari, Cagliari, Italy. 3FIDIA Farmaceutici, Abano Terme, Padua, Italy. Phosphatidylserine is a naturally occuring phospholipid wich is found in the cell membranes of a wide variety of organism from bacteria to man. The presence of phosphatidylserine in the neuronal membranes is not limited to a static structural function but it also important to the regulation of many metabolic processes, indicating that this phospholiopid may play a role in regulating crucial cerebral functions such as neuronal excitability, message tranduction, neurotransmitter activity and neuronal plasticity. Given that treatment with phospholipids improves brain neuron activity while pathological processes and/or natural aging reduce the renewal of the phospholipids membrane component, we used phospholipids liposomes, containing phosphotidilserine and phosphatidilcoline to prevent or ameliorate the negative effects of stress in neruronal plasticity. Neurogenesis and dendritic spine density were evaluated in stressed rats treated with liposomes. Liposomes were intraperitoneally administred (once of day) for 4 week in rats exposed to chronic unpredictable stress for 5 weeks. As expected the neureogenesis and dendritic spine density were decreased in rats exposed to chronic stress. On the contrary, liposomes treatment abolished the reduction of nerurogenesis and dendritic spine density elicited by chronic stress. Moreover, treatment with liposomes increased the density of dendritic spine in control not stressed rats. These results demonstrate that liposomes treatment has great efficacy in antagonizing the neurochemical and molecular consequences elicited by chronic exposure to stress in the brain. The mechanisms underlying the beneficial effects of liposomes might be mediated through actions exerted by phospholipids on neuronal membranes, neurotransmitters and/or interaction with trophic factors (NGF, BDNF). These mechanisms in turn might increase the efficacy of such treatment in people with impairment of cognitive function.

47. **Does exercise promote the expression of the resiliency factor Neuropeptide Y in the hippocampus of stressed mice?** Joyner, Tabitha; Alapati, Avani; Gerecke, Kim M. Rhodes College, Memphis, TN. Departments of Exercise potently protects the brain against the harmful effects of stress, via induction of a myriad of protective factors. One factor that is especially associated with neuroprotection is Neuropeptide Y (NPY). Chronic restraint stress (CRS) induces a toxic

microenvironment that recapitulates that seen in neurodegenerative diseases, and thus, may induce a vulnerability to developing these devastating disorders. We have previously shown that exercise protects against the neurotoxic effects of CRS via decreases in apoptotic Bax and reactive microglia. This work seeks to elucidate if the mechanism of this protection may be via increases in NPY in the hippocampus. As the Ca1 region is sensitive to chronic restraint stress, we hypothesize that there will be significantly lower NPY in the Ca1 of stressed sedentary mice, and that exercise will protect against this decrease. To investigate this, mice were randomly assigned to one of the four groups: Sedentary, Sedentary Stressed, Exercise, and Exercise stressed. All groups were housed two mice to each cage. Sedentary mice were in standard mouse caging, while those in the exercise group had free access to running wheels in their cages. After acclimating for two weeks, the mice in the stress conditions were placed into restrainers for two hours daily for fourteen days. The onset of each daily stress session was randomized during day light hours. On day fourteen, mice were euthanized, and the brains were perfused, collected, and processed for immunohistochemistry labeling. Preliminary data showed no significant difference in NPY expression between the four different groups in the Ca1 region of the hp. The dorsal region of the hp is more vulnerable to stress, compared to the more resilient ventral region. Therefore, we will continue to analyze the differences of NPY expression in the Ca1-4 regions, as well as in dorsal versus ventral hippocampus. Funding: Rhodes College Faculty Development Endowment Award.

48. **Habituation of the Startle Response in Zebrafish.** Blaser, R.E., Crawford, M., Muhammed-Menzies, D., University of San Diego. Habituation is one of the simplest forms of learning, and as such it provides an especially useful starting point for the characterization of learning in zebrafish. Additionally, the stimuli used here for habituation, a flash of LED light or a mild electrical shock, are also stimuli that may be used for studies of classical conditioning. Therefore, a thorough examination of their effects on zebrafish behavior is important for the design and interpretation of more complex learning experiments. We exposed adult zebrafish to a series of light flashes, or mild electrical shocks with varying inter-stimulus intervals. We determined that high-velocity swimming provides a clearer index of response to the stimuli than total distance or mean velocity. Additionally, we saw enhanced responding to the stimuli overall when the inter-stimulus interval was large, and a greater degree of habituation when the inter-stimulus interval was small.

49. **Differential Effects of Visual-Olfactory Maternal Presence Without Physical Contact on Behavior, Endocrine Response and Biogenic Amine Turnover**. Herod SM1, Bonnin A2. 1Azusa Pacific University, Dept. of Biology and Chemistry, Azusa, CA 91702-7000; 2Keck School of Medicine at the University of Southern California, Zilkha Neurogenetic Institute, Dept. of Cell & Neurobiology, Los Angeles, CA 90089-2821. The role of non-contact maternal presence in mitigating sensitivity to stress-induced disorders is incompletely characterized. In this study, we model the effects of a mild to moderate stressor during early adolescence in mice, with and without maternal presence. C57BL/6J experimental litters were bred in house and weaned at 3 weeks. At 3 weeks, baseline blood samples were collected under brief anesthesia and animals were randomly assigned to experience one of four conditions: no stress and same-sex littermate housing (ELS-), restraint stress for 3h/d, for 3 consecutive days (ELS+), an identical restraint stress with the mother present (ELS+Mom), or an identical restraint stress with a novel female present (ELS+Fem). Blood samples were collected following stress exposure to measure physiological corticosterone response. At 10 weeks all animals

experienced a 1 day, 3-hour stress challenge alone, regardless of early life stress condition. Behavior in open field, light/dark box, forced swim, and social choice was assessed at 11 weeks, followed by collection and microdissection of brain tissue into various regions at 12 weeks. ELS+Fem mice had a greater CORT response than ELS+ and ELS+Mom mice ($p=.025$) to adolescent stress, suggesting that the decreased CORT response of ELS+Mom mice was specific to the maternal relationship, however this effect did not persist into adulthood.). ELS+ mice showed resiliency to depressive-like behavior in the forced swim test ($p=.05$), and increased social behavior ($p=0.04$) that was not seen in other stress groups. All stressed groups had higher levels of 5-HIAA (serotonin metabolite) in brainstem, hypothalamus, and cortex (all $p<0.05$), higher DOPAC (dopamine metabolite) in the brainstem ($F=6.20$, $p=0.04$) and higher HVA (catecholamine metabolite) in the hippocampus ($F=36.82$, $p=0.001$) as compared to non-stressed controls. While non-contact maternal presence is sufficient to mitigate the HPA axis response in the short term, adolescent stress experienced even in the presence of a maternal relationship influences long-term effects on behavior and brain development. These findings indicate differential effects of non-contact maternal presence, and suggest an interactive effect of development.

50. **Ephedrine HCL, Curcumin and Turmerone in Neurogenesis and Inhibition of Beta-Amyloid Plaques in Transgenic Mice Models**. Paramasivam,Keerthi1. Harvard Medical School1. This study was done to demonstrate the effects of Ephedrine HCL ,Turmerone & Curcumin in Neurogenesis and Inhibition of Beta Amyloids in Transgenic Mice. The transgenic mice models used contain mutations associated with familial Alzheimer's disease (APP Swedish,MAPT P301L,and PSEN1 M146V). These mice develop age-related, progressive neuropathology including plaques and tangles. Ten-month-old male and female APPSw Tg+ and Tg− mice from 12 litters were randomly split between treatment groups. Tg+ mice were fed either chow containing a low dose of curcumin (160 ppm;n=9; a high dose of curcumin (5000ppm;n=6), or no drug (n=8) for 6 months. Mice with low and high dose of curcumin were given specific doses of 0.02% Ephedrine HCL injection every 72 hours and underwent a single intracerebroventricular injection of 3mg ar-turmerone. To evaluate whether curcumin treatment affected plaque pathology, cryostat hemibrain sections from Tg+ control and Tg+ low-dose curcumin-treated mice were immunostained with an antibody against Aβ1–13(DAE). Two-factor ANOVA revealed a significant reduction in plaque burden in curcumin, Ephedrine HCL and turmerone treated animals ($F(1,60) = 4.74$; $p=0.03$), in which amyloid burden was decreased by 43.6% in treated animals compared with untreated animals. Soluble Aβ in Tg+ untreated and Tg+ low-dose curcumin mice were measured by sandwich ELISA. Two-way ANOVA showed significant treatment effects in decreasing the levels of soluble Aβ ($*p < 0.05$). Underlying mechanistic pathways that might link curcumin treatment to increased cognition and neurogenesis via exon array analysis of cortical and hippocampal mRNA transcription showed a positive result.

51. **Subthalamic stimulation ameliorates hyperkinetic movement disorders**. Kuo, C-C1,2, Tai, C-H2. 1Department of Physiology, National Taiwan University College of Medicine, 2Department of Neurology, National Taiwan University Hospital. Deep brain stimulation (DBS) with injection of depolarizing currents into the subthalamic nucleus (STN) is an important advance for the treatment of Parkinson's disease (PD), a prototypical hypokinetic movement disorder. On the other hand, chorea, ballism and dystonia are the most typical examples of hyperkinetic movement disorders. It is postulated that there are decreased activities of both hyperdirect and indirect pathways in the

cortico-subcortical re-entrant loops (cortex-basal ganglia-thalamus-cortex circuits), causing increased activities in the direct pathway and consequently uncontrollable and "excessive" movements. The success of DBS of STN in PD implicates that STN takes an important or even pivotal position in both hyperdirect and indirect pathways. It is therefore desirable to investigate the role of STN in hyperkinetic movement disorders. We have shown that normal animals can be rendered hypokinetic with hyperpolarizing currents injected into STN. We further investigated the behavioral and electrophysiological effect of injection of hyperpolarizing currents into the STN on two different types of hyperkinetic animal models. The two models are the levodopa-induced hyperkinetic model in parkinsonian rats and the intra-striatal injection of 3-nitropropionic acid-induced hyperkinetic model, chosen for the putative coverage of both neurodegeneration-related and neurotoxin-induced cortico-basal ganglia circuit derangement. Injection of hyperpolarizing currents into STN readily alleviated the hyperkinetic behaviors in both animal models, with increased burst discharges recorded in the STN. Application of hyperpolarizing current into STN via DBS electrode could be a promising therapy for a relatively wide spectrum of hyperkinetic movement disorders.

52. **Effects of caffeine on compulsive-like and anxiety-like behaviors in a non-induced mouse model of Obsessive Compulsive Disorder**. Vanessa Santana[1], Tandi Marth[1], Brooks Poe[1], Adam Hall[1], McKenzie Sweeney[1], Swarup Mitra[1], Abel Bult-Ito[1], [1]University of Alaska Fairbanks. Obsessive-compulsive disorder (OCD) is a psychiatric disorder in which patients have reoccurring compulsive behaviors and obsessions that interfere with their quality of life. OCD is also associated with other comorbidities such as anxiety and depression and can be aggravated by common environmental exposures such a caffeine consumption. The specific mechanism by which caffeine acts to produce these effects remain unclear. Past studies have indicated that caffeine may increase the availability of D2/D3 receptors while blocking adenosine receptors in humans. In mice, caffeine has found to influence depression and memory deterioration via adenosine A2A receptors. This study used a non-induced mouse model of OCD, which was developed by selective breeding of mice for compulsive-like nest building behavior, to identify alterations in neuronal pathways caused by caffeine in this model. The two strains of mice in this model also present compulsive-like marble burying behavior. In the first part of this study, we determined the effects of high (25 mg/kg) and low (3 mg/kg) doses of caffeine on anxiety-like and compulsive-like behaviors in the two strains of compulsive-like mice. In the second part of this study we evaluated the mechanisms by which these effects occur by giving the mice intraperitoneal injections of a dopamine D2/D3 receptor antagonist or an adenosine A2A receptor agonist prior to testing. The nest building and marble burying tests were used to measure compulsive-like behaviors, the open field test was used to measure anxiety-like behaviors in the mice. In part 1, strain and caffeine dose effects on anxiety-like behaviors were both observed. Caffeine was also found to increase compulsive-like behaviors: a strain effect was observed in the nest building test at high doses and both strain and dose effects were observed in the marble burying test. During part 2, the group that was treated with the high dose of caffeine and the dopamine D2/D3 receptor antagonist presented decreased compulsive-like behaviors in both the nest building and the marble burying tests. The group that was treated with the high dose of caffeine and the adenosine A2A receptor agonist decreased their compulsive-like behaviors in the first 3 hours of the nest building test, but then increased these behaviors over the course of 24 hours. Supported by the University of Alaska Fairbanks Biomedical Learning and Student Training Program.

53. **Role of enkephalin in dopamine2-receptor expressing neurons in licking microstructure.** Ian A. Mendez1, Hoa A. Lam1, Stephanie N. Lee1, James Boulter1, Sean B. Ostlund2, Niall P. Murphy1, and Nigel T. Maidment1. 1Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human, University of California Los Angeles, Los Angeles, CA USA. 2Department of Anesthesiology and Perioperative Care, University of California at Irvine, Irvine, CA, USA. Opioid signaling is implicated in mediating the hedonic and motivational aspects of palatable foods. When licking for palatable solutions, global enkephalin knockout mice emit fewer bouts of licking than wildtypes, but similar bout lengths. Interestingly, the number of times a mouse engages in a new bout of licking is suggested to reflect motivational aspects of feeding behavior, while the length of the bout once engaged is determined primarily by the immediate hedonic impact of the food stimulus. Objective: In these studies, we investigated the role of endogenous enkephalin, specifically in neurons expressing dopamine D2 receptors, in licking microstructure. Design: D2 specific proenkephalin knockout mice (D2 PENK KO) and their wild-type littermates were trained to lick for 20% sucrose for 5 days in a lickometer. Subsequently, the effects of sucrose concentration (2% versus 20%) and hunger state (4 h versus 18 h food deprivation) were assessed. A second group of D2 PENK KO and wildtype mice were trained to lick for 20% sucrose for 7 days. Following training in these mice, the hypophagic effects of 5mg/kg naltrexone on licking were assessed. Results: Compared to wildtype mice, D2 PENK KO mice displayed fewer total licking bouts, but similar mean bout lengths, across sucrose concentrations and hunger states. In the second group of mice, naltrexone decreased total bout number in wildtype mice, but had no effect on mean bout length. No effects of naltrexone were observed in D2 PENK KO licking behavior. Discussion: Similar to previous observations in global PENK KO mice, D2 PENK KO mice emitted fewer bouts of licks, but similar licking bout lengths. Naltrexone hypophagia was driven by decreases in the number of licking bouts, an effect that D2 PENK KO mice were insensitive to. Overall these findings suggests that enkephalin, specifically in D2 expressing neurons, plays an important role in establishing feeding patterns, and may therefore play a role in psychopathological conditions characterized by aberrant feeding behavior. Supported by Grant #: DA05010.

54. **Disruption of autophagic signaling in murine forebrain affects excitatory-inhibitory balance via mistrafficking of GABAA receptors leading to ASD-like behaviours**. Kelvin Hui1, Noriko Takashima1, Hiroshi Matsukawa1,3, Akiko Watanabe2, Per Nilsson4, Ryo Endo1, Takaomi Saido4, Shigeyoshi Itohara3, Takeo Yoshikawa2, Motomasa Tanaka1. 1Laboratory for Protein Conformation Diseases, RIKEN Brain Science Institute. 2Laboratory for Molecular Psychiatry, RIKEN Brain Science Institute. 3Laboratory for Behavioral Genetics, RIKEN Brain Science Institute. 4Laboroatory for Proteolytic Neuroscience, RIKEN Brain Science Institute. Many monogenic forms of autism spectrum disorder (ASD) are known to affect the mTOR signaling pathway, involving mutations in PTEN, TSC1, TSC2, and FMR1 genes. While recent work has focused on the dysregulation of protein translation via the deletion of these genes, few studies have examined how disruption of autophagy, another major downstream branch of mTOR signaling, contributes to neuronal dysfunction and ASD pathogenesis. To this end, we and others have previously examined mice deficient for autophagy in forebrain excitatory neurons via the deletion of Atg7 by CaMKII-cre and observed ASD-like behavioural abnormalities in addition to neuronal dysfunctions from the molecular to the network level. As ASD is believed to be caused by an imbalance between excitatory and inhibitory signals in the brain, we have further extended our analysis to examine disruption of autophagy in forebrain GABAergic

interneurons. Similar to disrupted autophagy in other neuronal and non-neuronal cell types, Atg7 deletion by Dlx5-cre results in time-dependent ubiquitin+ and p62+ aggregate formation in affected neurons in the cerebral cortex, hippocampus, and striatum. Interestingly, with some minor differences, Dlx5-cre Atg7 cKO mice primarily exhibit a similar set of ASD-like behavioural abnormalities previously observed in CaMKII-cre Atg7 cKO animals. Furthermore, consistent with a specific defect on GABAergic interneurons, we have detected a shift in the excitatory-inhibitory balance in the hippocampi of these knockout mice. Using primary neuron cultures, a reduction in the surface expression of GABAA receptor subunits was observed in Atg7 cKO neurons. Mass spectrometry and immunoblotting analyses of GABARAPL2, a member of the GABARAP (GABA receptor-associated protein) protein family, revealed that it accumulates in and shifts into the higher molecular weight fraction in both CaMKII-cre and Dlx5-cre Atg7 cKO brains. Knockdown of GABARAPL2 in wild-type primary neurons similarly showed reduced surface expression of GABAA receptors, thus suggesting that the loss of functional GABARAPL2 in Atg7 cKO neurons may be the causal link to the disruption of E-I balance and abnormal ASD-like behaviours observed in Atg7 cKO mice. K.H. was a recipient of the JSPS Postdoctoral Fellowship for Foreign Researchers and a member of the RIKEN Foreign Postdoctoral Researcher program.

THURSDAY, June 29

Keynote Speaker

08:00-09:00 **Dopamine in schizophrenia: from bedside to bench and back**. Abi-Dargham, Anissa. *Setouchi Hall, Room 1-2*

Dopamine in schizophrenia: from bedside to bench and back. Anissa Abi-Dargham, MD. Stony Brook University. The dopamine (DA) dysfunction in schizophrenia consists in a topographically precise sets of alterations, documented across multiple labs with Positron Emission Tomography (PET) imaging studies, that showed excess striatal dopamine synthesis, release, and D2 supersensitivity [1]. Recent data suggest also profound extrastriatal deficits in DA release [2]. The presence of opposing findings of striatal excess and extrastriatal deficit including midbrain deficit is puzzling as it suggests that striatal excess may not be a consequence of midbrain DA cells overactivity. These studies in humans have led to translational studies in animal models to understand the cellular mechanism at play. In particular the D2 overexpressing (D2OE) [3] mouse, developed to model the well established finding of excess striatal D2 stimulation, has shown that cortical dependent cognitive deficit and abnormal cortical DA signaling can be a consequence of developmental abnormalities in striatal D2 stimulation. Findings from this mouse model or altered circuitry within the basal ganglia pathways are currently under testing in patients in studies of "reverse translation". Another line of research resulting from human imaging studies is the focus on local regulation of dopamine release within the striatum that may explain the localized excess dopamine release to the striatum. Since many developmental factors, both genetic [4] and environmental, have been shown to be at play in schizophrenia, and shown to affect dopaminergic indices, these combined lines of evidence suggest that DA dysfunction may be an early event leading to profound consequences on the rest of the circuitry and behavior.

1. Weinstein, J.J., et al., *Pathway-Specific Dopamine Abnormalities in Schizophrenia.* Biol Psychiatry, 2016.
2. Slifstein, M., et al., *Deficits in Prefrontal Cortical and Extrastriatal Dopamine Release in Schizophrenia: A Positron Emission Tomographic Functional Magnetic Resonance Imaging Study.* JAMA Psychiatry, 2015.
3. Kellendonk, C., E.H. Simpson, and E.R. Kandel, *Modeling cognitive endophenotypes of schizophrenia in mice.* Trends Neurosci., 2009. **32**(6): p. 347-58.
4. Schizophrenia Working Group of the Psychiatric Genomics, C., *Biological insights from 108 schizophrenia-associated genetic loci.* Nature, 2014. **511**(7510): p. 421-7.

09:30-11:30 **Symposium: Norepinephrine and executive function: Recent findings.** Chairs: Barry Waterhouse and Jill McGaughy. *Setouchi Hall, Room 1-2*

Correlation between psychostimulant-induced alterations of local field potentials within primary visual circuits and improved performance of a sensory signal detection task. Rachel L. Navarra1,2, Brian D. Clark1,2, Barry D. Waterhouse1,2. 1Rowan University School of Medicine, 2Drexel University College of Medicine. Methylphenidate (MPH) is a psychostimulant used clinically to treat attention deficit hyperactivity disorder (ADHD) and off-label as a performance enhancing drug by healthy individuals. MPH enhances catecholamine transmission via blockade of norepinephrine and dopamine transporters, but how this action impacts neural circuits responsible for cognitive and sensorimotor functions to improve performance is unclear. We previously reported that MPH enhances neuronal responses to visual stimuli

within the rat dorsal lateral geniculate nucleus (dLGN) while improving the speed to make correct responses during performance of a visual signal detection task. Here, we investigated a range of MPH effects on behavioral outcomes and measures of local field potentials (LFPs) in the dLGN during performance of the task. P30, the first positive deflection of the visual evoked potential (VEP) produced in response to task-related visual stimuli, was reduced in latency and amplitude following MPH administration. Across animals there was a significant positive correlation between P30 latency and latency to make correct responses, where the fastest times were found with MPH. Further, MPH increased coherence between LFPs at theta frequencies, which have been linked to variations in cognitive and sensorimotor processes. Thus, it appears MPH speeds, strengthens, and better integrates signals within the dLGN; effects that are consistent with faster sensory signal processing and better visual signal detection. To our knowledge this is the first demonstration of a direct correlation between electrophysiological measures of sensory processing in a primary thalamic relay circuit and behavioral outcomes in a visual signal detection task. These results have led to the generation of a theoretical model in which MPH manipulates noradrenergic mechanisms to create optimal conditions for enhanced processing of sensory information. Sensory information is then transmitted to decision making circuits with greater speed and strength to result in more efficient behavioral responses. This work suggests that MPH-induced sensory enhancement may be a significant component of psychostimulant-mediated performance enhancement in ADHD patients and healthy individuals. Funding support: PhRMA Foundation Pre-Doctoral Award (Rachel Navarra), NIH/NIDA NRSA F31DA037651 (Rachel Navarra), NIH/NIDA R01 DA017960 (Barry Waterhouse, PI).

Development of noradrenergic innervation of prefrontal cortex contributes to the ontogeny of executive control during adolescence. J. McGaughy1 1. University of New Hampshire Rodent models of executive control in adolescents have focused on immature response inhibition resulting from different maturational rates for the mesolimbic and mesocortical dopaminergic systems. Specifically, the earlier maturation of the mesolimbic system leads to processing of rewarding stimuli prior to the full development of the mesocortical system hypothesized to allow inhibitory control. As a result, adolescents have difficulty adapting to circumstances where reinforcement contingencies have changed, e.g. reversal learning or extinction. However, other immaturities in adolescent executive control may result from the late development of cortiopetal noradrenergic systems. Recent anatomical studies have shown that norepinephrine transporter density is higher in the prefrontal cortices of adolescent rats relative to adults. This higher density of norepinephrine transporter is hypothesized to produce sub-optimal levels of norepinephrine in adolescent rats. Transporter density has been found to differ among sub-regions of the prefrontal cortex and to change during adolescence. Behaviorally, adolescent rats are more distractible and yet more cognitively rigid than adults. Drugs that increase cortical norepinephrine improve attentional performance of adolescent rats. Interestingly, these same drugs given to adults can impair attentional performance. Systemic administration of methylphenidate to distractible adolescent rats improves attentional focus in a test of attentional set formation and shifting. Because damage to the anterior cingulate cortex can produce similar impairments in this form of distractibility, this region is the presumed target for the effects of methylphenidate. Cognitive rigidity can be attenuated by systemic administration of atomoxetine to adolescents and facilitate shifts of attentional set. Noradrenergic lesions of the prelimbic cortex produce cognitive rigidity providing support for the hypothesis that the effects of atomoxetine result from effects in this region. Together these data highlight the need to understand the specific neural circuits that contribute to distinct aspects of executive control and to investigate the contributions of neuromodulatory systems beyond ascending dopaminergic pathways.

Anatomical, elelctrophysiological, and molecular evidence for heterogeneous organization and modular operation of the locus coeruleus-noradrenergic system. Barry Waterhouse1,2, Daniel Chandler1,2 1Rowan University School of Osteopathic Medicine, 2Drexel University College of Medicine. The nucleus locus coeruleus (LC) innervates the entire rat neocortex and through its primary transmitter, norepinephrine (NE), exerts a modulatory influence on executive function, sensory signal processing, and motor network operations. In contrast to the conventional view of the LC-NE system as broadly projecting and homogeneous in operation, several lines of evidence suggest that LC projections are segregated, anatomically and functionally, with respect to forebrain terminal fields. First, unbiased stereological analyses of DBH-positive varicosities in rat cerebral cortex reveal a higher density of noradrenergic varicosities in prefrontal vs motor, somatosensory, and piriform cortices. Second, conventional retrograde labeling studies have shown that LC-NE projections to prefrontal cortical sub-regions and motor cortex arise from segregated sub sets of LC neurons. These subsets of cells display unique molecular and electrophysiological profiles with respect to their efferent targets. Third, viral vector tracing experiments in transgenic mice reveal an intranuclear distribution of LC projection neurons that also reflects an efferent topography with respect to forebrain targets. Collectively these data argue for a more selective mode of NE release and regulation of target circuit operations. As such, these findings have prompted the generation of a model that incorporates these organizational features into a scheme that provides for a more sophisticated modular operation of the LC-NE system than has been previously appreciated. In simplistic terms the model proposes LC output as capable of sequentially optimizing cognitive and motor network operations such that executive control and subsequent motor responses in adaptive behaviors are biased in favor of deciding before acting. Funding support: NIH NIMH R01 MH101178 (Barry Waterhouse, PI) and an award from the Drexel University Human Cognition Enhancement Program (Daniel Chandler, PI).

Modafinil improves cognitive control in humans without inducing hyperactivity. Zackary A. Cope1, Arpi Minassian1,2, Dustin Kreitner1, David A. MacQueen1,3, Morgane Milienne-Petiot1,4, Mark A. Geyer1,3, William Perry1, and Jared W. Young1,3. 1 Department of Psychiatry, School of Medicine, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA 92093-0804. 2 Center for Stress and Mental Health (CESAMH), VA San Diego Healthcare System, San Diego, CA. 3 Research Service, VA San Diego Healthcare System, San Diego, CA. 4 Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands. The wake-promoting drug modafinil is frequently used off-label to improve cognition in psychiatric and academic populations alike. The domain specific attentional benefits of modafinil have yet to be objectively quantified in healthy human volunteers using tasks validated for comparison across species Such quantification is required to determine its mechanism of effect since it is a low-affinity inhibitor for the dopamine and norepinephrine transporters (DAT/NET respectively), and is thought to act via the locus coeruleus (Minzenberg and Carter, 2008). Additionally, given DAT effects it is unclear if any effects are attributable to a non-specific increase in arousal, a feature of many catecholamine reuptake inhibitors (e.g., cocaine, amphetamine). Here, we tested for domain-specific enhancement of attention and cognitive control by modafinil (200 and 400 mg) in healthy volunteers using the 5-choice continuous performance task (5C-CPT) and Wisconsin Card Sort Task (WCST). An additional cross-species assessment of arousal and hyperactivity was performed in this group and in mice (3.2, 10, or 32 mg/kg) using species-specific versions of the behavioral pattern monitor (BPM). Modafinil significantly enhanced attention (d prime) in humans performing the 5C-CPT ($F(2,58)=4.4$, $p<0.05$, partial $\eta 2 =0.18$) at doses that did not affect WCST performance or induce hyperactivity in the BPM ($F<1.95$, ns). This improvement was driven by a strong trend towards increased hit rate, representing improved target detection ($F(2,58)=2.8$, $p=0.07$,

partial η2 =0.019). In mice, modafinil increased activity in the BPM ($F(3,55)=10.2$, $p<0.001$, partial η2 = 0.36), but only at the highest dose. These results indicate that modafinil produces domain-specific enhancement of attention in humans not driven by hyperarousal, unlike other drugs in this class, and higher equivalent doses were required for hyperarousal in mice. Further, these data support the utility of using the 5C-CPT across species to more precisely determine the mechanism(s) underlying the pro-cognitive effects of modafinil, testing potential dopaminergic vs. noradrenergic mechanisms.

09:30-11:30 **Symposium: Neuropeptide modulation of addiction.** Chairs: Elvan Djouma and Andrew Lawrence. *Setouchi Hall, Room 6*

Peptide Interactions and Reward-Seeking Behaviour. Andrew J Lawrence, Florey Institute of Neuroscience & Mental Health, University of Melbourne, Victoria, Australia. Relapse and hazardous drinking represent the most difficult clinical problems in treating patients with alcohol use disorders. Increasing our understanding of the brain circuits and chemicals that regulate alcohol intake and relapse offers the potential for more targeted therapeutic approaches to assist in relapse prevention. Stress is a key precipitant of relapse, and relaxin-3 signalling modulates both stress responses and alcohol intake. We therefore examined a role for the relaxin-3 system in alcohol-seeking. In iP rats, icv microinjection of a selective RXFP3 antagonist prevented yohimbine-induced reinstatement of alcohol-seeking, discrete microinjections implicated both the dorsal BNST and central amygdala as loci. Relaxin-3 neurons are predominantly located in the pontine nucleus incertus (NI) which is highly sensitive to CRF. Intra-NI microinjection of a selective CRF1 receptor antagonist (CP376395) attenuated yohimbine-induced reinstatement of alcohol-seeking whereas the CRF2 receptor antagonist (Astressin-2B) had no effect. After long-term voluntary alcohol intake in iP rats, qPCR revealed that the expression of mRNA encoding both CRF1 and RXFP3 receptors was upregulated in the NI. We also found expression of the mRNA encoding CRF within the NI, which was confirmed with immunohistochemistry in both iP rat brain and CRF-Cre x TdTomato reporter mice. These data suggest NI neurons contribute to reinstatement of alcohol seeking, via an involvement of CRF1 signaling. Furthermore, chronic ethanol intake leads to neuroadaptive changes in CRF and relaxin-3 systems within rat NI. The NI also receives orexinergic innervation and so we undertook analogous experiments. Bilateral NI injections of the OX2 receptor antagonist TCS-OX2-29 attenuated yohimbine-induced reinstatement of alcohol seeking, while the OX1 receptor antagonist SB-334867 had no effect. In line with these data, orexin-A depolarized NI neurons recorded in coronal brain slices, sensitive to bath application of TCS-OX2-29, but not SB-334867. These data suggest an excitatory orexinergic input to NI contributes to yohimbine-induced reinstatement of alcohol seeking, predominantly via local OX2 receptor signalling. Collectively, these data implicate CRF and orexin inputs to relaxin-3 neurons of the NI in alcohol-seeking.

Stress and potent-rewards remodel lateral hypothalamic orexin circuits. CV Dayas1, BA Graham, MH James, EJ Campbell, JW Yeoh. University of Newcastle & Hunter Medical Research Institute, NSW, Australia. Early life stress and exposure to drugs of abuse increases the risk of developing mood disorders such as anxiety and depression. We have been investigating how these stimuli provoke synaptic changes in the lateral hypothalamus (LH), a region known to control motivated behaviours. Within the LH we have focused on the orexin system as it has been implicated in mood-relevant behaviours including anxiety, stress reactivity and reward-seeking. Using electrophysiology, immunohistochemistry and models of reward-seeking, we have found evidence that chronic self-administration of cocaine enhanced plasticity at excitatory synapses in LH orexin circuits. Further, we uncovered an important role for group III (GP III) metabotropic glutamate receptors (mGluRs) in gating excitatory drive to LH-orexin neurons. We

hypothesise that GP III mGluRs act as a metaplastic switch, controlling plasticity at excitatory synapses onto orexin neurons and that potent reward experiences such as high fat food and exposure to drugs of abuse dysregulate this mechanism. This dysregulation leaves excitatory input to LH orexin neurons unchecked to drive pathological reward seeking. Supporting this conclusion, intra-LH treatment with a GP III mGluR agonist suppressed drug-seeking for cocaine. With respect to stress, we have found that a period of maternal separation in early life produced an opposite pattern of rewiring in LH and promoted reduced reward-seeking for sucrose on a progressive ratio schedule of reinforcement. Chemogenetic activation of LH cells using DREADD recovered this behaviour and increased the activity of LH neurons including those that express orexin. Together, these data suggest that while stress and drug taking have a profound impact on LH circuits and associated behaviours, chemogenetic and pharmacological approaches can reset dysfunctional LH circuits offering potential entry points for therapeutics. Supported by grants from HMRI and NHMRC of Australia.

Characterisation of the galanin-3 receptor in drug-seeking behaviour. Elvan Djouma. School of Life Sciences, La Trobe University, Bundoora, Australia 3086. Galanin is a neuropeptide that has been critically implicated in mediating addiction. More specifically, we have shown administration of the galanin receptor-3 (GALR3) antagonist, SNAP 37889, reduces alcohol-seeking and cue-induced relapse in an operant paradigm in rats and reduces morphine self-administration in mice, independent of alterations in locomotor activity or anxiety-like behaviour. Using the Scheduled High Alcohol Consumption (SHAC) procedure, we have also shown that SNAP 37889 (30 mg/kg, i.p.) treated mice drink significantly less ethanol, sucrose and saccharin than vehicle treated mice. A lack of difference in the rate of hepatic ethanol metabolism between SNAP 37889 and vehicle treated mice further suggests that the decrease in ethanol intake via SNAP37889 is centrally mediated. Recently, generation of novel GALR3 knockout (KO) mice has allowed us to further characterise the role of this receptor in drug-seeking behaviour by comparing ethanol preference and motivation to obtain alcohol in GALR3 KO and wildtype (WT) littermate controls. Interestingly, both male and female GALR3 KO mice displayed a significant preference and increased intake for ethanol over water, when compared to WT littermates in the two bottle free choice paradigm. Mice were also screened for anxiety through elevated plus maze and pre-pulse inhibition tests. Learning and cognition were evaluated by Y-maze and fear conditioning. Social interaction testing was used to establish any genotype differences in social affiliation and locomotor chambers were used to investigate differences in amphetamine-induced locomotor activity. No significant genotype differences were revealed in any of these behavioural tests, suggesting that the increased ethanol consumption observed in GALR3 KO mice was not due to behavioural deficits. Overall, GALR3 ablation results in increased alcohol consumption which is in contrast to the previous effects observed when acutely blocking GALR3 pharmacologically in different addiction paradigms using both rats and mice. This work was funded by the Research Focus Area, Understanding Disease, at La Trobe University.

The role of orexin and dynorphin in modulating mesolimbic dopaminergic projections. Baimel, C., 1 Lau, B.K.,1 Qiao, M.,1 Borgland, S.L.1. 1The Hotchkiss Brain Institute, University of Calgary, 3330 Hospital Dr. NW, Calgary, AB T2N 4N1 CANADA. Orexin (hypocretin) and dynorphin are neuropeptides with opposing actions on motivated behavior. Despite their opposing actions, these peptides are packaged in the same dense core vesicles within the hypothalamus, the sole source of orexin in the brain. Furthermore, both peptides have receptors on VTA dopamine neurons, and activation of their respective orexin or kappa-opioid receptors induces opposing modulatory actions on firing activity of VTA dopamine neurons. Inhibition of orexin receptors in the VTA disrupts drug seeking. This effect can be blocked by pretreatment

with the Kappa-opioid receptor antagonist, suggesting that in the absence of hypocretin signaling, the inhibitory effects of dynorphin on motivated behaviour are unopposed. Using retrograde labels to identify projection targets of VTA dopamine neurons, we tested how orexin and dynorphin modulated each of these dopaminergic circuits. We found that BLA projecting and NAc lateral or medial shell projecting dopamine neurons are electrophysiologically distinct and non-overlapping populations. Furthermore, orexin primarily activates VTA dopamine neurons that project to the medial or lateral shell of the nucleus accumbens, where as dynorphin primarily inhibits dopamine neurons projecting to the basolateral amygdala. We propose that through corelease of orexin A and dynorphin, orexin projections coordinate the activity of VTA dopamine neurons by modulating distinct circuits to drive motivated reward seeking behaviour.

13:30-15:00 **Symposium: Experimental reproducibility: Opportunities over crisis.** Chairs: Jill Silverman and Stacey Rizzo. *Setouchi Hall, Room 6*

Lack of generalization of strain and sex across behaviors? data from the founder strains of the collaborative cross and diversity outbred mouse populations. Stacey J. Sukoff Rizzo and Kristen D. Onos. The Jackson Laboratory Center for Biometric Analysis. Inbred mouse strains have been a powerful tool for decades, helping to unravel the underpinnings of biological problems and employed to evaluate potential therapeutic treatments in drug discovery. While inbred strains such as the C57BL/6 demonstrate relatively reliable and predictable responses in traditional behavioral assays, using a single inbred strain alone or as a background to a mutation, is analogous to running a clinical trial in a single individual and their identical twins. The most common human diseases are caused by complex etiologies and a single inbred strain is not representative of the genetically diverse patient populations. Recently, Sittig and colleagues (2016) demonstrated that genotype-phenotype relationships should not be expected to generalize to other inbred strains and therefore the assumption that data generated in a single inbred strain is less as likely to generalize to human patients. To this end, as a way to capture genetic diversity, researchers are now beginning to include panels of inbred strains to evaluate single mutations across, and large recombinant inbred panels such as the Collaborative Cross (CC) are also available for this purpose. The CC was developed through a large consortium as a strategy to rapidly and randomly mix the genomes of eight common strains including two strains with high incidence of developing cancers (A/J and 129S1/SvImJ), two strains that develop diabetes (NOD/LtJ and NZO/H1LtJ), three wild-derived strains (CAST/EiJ, PWK/PhJ, and WSB/EiJ) and C57BL/6J (Churchill et al. 2004). As a prelude to evaluating CC lines in our laboratory, we endeavored to understand the baseline behavioral responses in both sexes of each of the eight founder strains of the CC through a battery of traditional behavioral tests. These data will better put into perspective the lack of generalization of phenotypes across standard behavioral assays that have been developed and optimized for C57BL/6 mice and will also highlight substrain differences across C57BL/6 that likely impact cross-laboratory reproducibility.

Do Rats Rule for Neurodevelopmental Disorders? Evidence from the Shank3 Mutant Rat Model of Phelan-McDermid Syndrome and Autism Spectrum Disorder. Jill L Silverman, Elizabeth L Berg and Markus Woehr. Mutations in the SHANK3 gene lead to autism spectrum disorder (ASD), Phelan-McDermid Syndrome (PMS), as well as intellectual disabilities (Betancur & Buxbaum, 2013; Gauthier et al., 2009; Leblond et al., 2014; Moessner et al., 2007). Reduced expression of SHANK3, which codes for a synaptic scaffolding protein, has been hypothesized to lead to impairments in key brain functions underlying social communication and cognition (Durand et al., 2007). Both mutant mouse and, more recently, rat models have been generated in an effort to assess the neurobiological and behavioral effects of mutations in

SHANK3 (Yang et al., 2012; Peca et al., 2011; Kouser et al., 2013; Jaramillo et al., 2016; Zhou et al., 2016; Harony-Nicholas et al., 2016). The present experiments aimed to evaluate various aspects of development, social communication, and corresponding neural correlates using sophisticated tools and taking advantage of the only generated rat model of Shank3 mutations, to date, by carrying out studies across early life and in critical juvenile developmental windows. Benefits of the rat that we have observed, over the mouse include (i) rats possess a richer behavioral repertoire compared to mice, (ii) rats exhibit more behavior during critical developmental time periods such as juvenile ages, and (iii) their larger size makes it easier to carry out detailed anatomical and physiological measurements analogous the corresponding human condition. We found subtle social deficits in the Shank3 rat model by presenting individual rats with a natural 50-kHz USV versus an acoustic control stimulus, and comparing subsequent USV production and approach behavior toward the stimulus source. However, we found normal juvenile sociability assessed via the three-chambered social approach assay in which rats could choose to interact with a novel object or a novel conspecific, in a social novelty assay in which rats could choose to interact with a familiar or a novel conspecific, and a play-promoting reciprocal social interaction assay in which rats could freely engage with a novel wildtype (WT), sex-matched conspecific. We conclude that rats have better signal detection for subtle sophisticated behavior, and that ankryn domain Shank3 mutations cause minor deficits only detectable in the rat models. We further conclude that the richer repertoire and sophisticated developmental interactions adds elements of complexity over mouse models that will need to be further investigated. Finally, we reproduced earlier findings by Harony-Nicholas et al., 2016, suggesting that rats may have lower inherent variability and better reproducibility than mouse models. The data presented here lend support for the important role of Shank3 in social communication and for the use of transgenic rat models as tools to study the neurobiology underlying the behavioral phenotypes in neurodevelopmental disorders.

Reproducibility of reduced dopamine transporter function recreating bipolar mania-relevant behavior. Jared W. Young1,2, Zackary A. Cope1, Molly Kwiatowski1, William Perry1, Arpi Minassian1, Mark A. Geyer1,2. 1 Department of Psychiatry, School of Medicine, University of California San Diego. 2 Research Service, VA San Diego Healthcare System, San Diego, CA. Developing targeted therapeutics for psychiatric disorders first requires an understanding of the neural mechanisms underlying abnormal behavior. Animal models are required to determine the effects of mechanisms putatively underlying psychiatric conditions. Such models also enable the testing of targeted potential therapeutics. To-date however, the reproducibility of animal models of diseases have been called into question. Our team has investigated the neural mechanisms underlying bipolar disorder (BD) for some time. Dopamine is a major neurotransmitter implicated in several neuropsychiatric disorders, whose homeostasis is controlled primarily via the dopamine transporter (DAT). Polymorphisms in DAT have been linked to numerous psychiatric disorders (Greenwood et al, 2001), although specifically reduced expression was observed in unmedicated euthymic bipolar disorder sufferers (Anand et al, 2011). Using the same cross-species multivariate assessment of exploratory behavior – the behavioral pattern monitor (BPM; Geyer et al, 1986) – we showed that acutely ill BD mania patients exhibit a BPM pattern of hyperactivity, hyperexploration, and straighter line movements (reduced spatial d; Perry et al, 2009). We then demonstrated that severely reducing DAT function in knockdown (KD) mice recreated this exploratory profile (Perry et al, 2009). We have since recreated these findings in numerous cohorts (Perry et al, 2009; Young et al, 2010; 2011; van Enkhuizen et al, 2013a; 2014). This effect has been observed when backcrossed onto both 129 and C57BL/6 background strains (Perry et al, 2009; van Enkhuizen et al, 2013). Hence, irrespective of background strain, reduced DAT functioning recreates BD mania profile of

hyperexploration. Importantly, we have also shown that chronic treatment with currently used BD treatments valproate and lithium partially attenuate this profile in mice as also seen in BD mania patients (van Enkhuizen et al, 2013b; Milienne-Petiot et al, 2017; Minassian et al, 2013). Effect sizes of these differences are consistent across these tests, with Cohen's d effect sizes for hyperactivity ranging from 1.3 – 1.7, comparable to the first publication with these mice in a different laboratory (a Cohen's d effect size 1.6; Zhuang et al, 2001). The additional measures of hyperexploration and straight-line moving from the BPM provide similar effect size ranges in DAT KD mice compared with their wildtype littermate mice (0.5 – 0.7 and 0.4 – 1.1). Hence, not only does reduced DAT functioning recreate BD mania exploratory profile, but is consistent across cohorts, and is treatable in-part via BD-specific maintenance treatments. These mice are therefore a highly reproducible model for aspects of BD mania. Novel targeted therapeutics for BD mania can therefore likely be generated using this model, with such studies ongoing (Milienne-Petiot et al, 2017b). Future studies are also ongoing to determine mechanistic alterations in other neurotransmitter systems that might contribute to the observed behaviors, enabling the identification of potentially novel therapeutics not targeting the dopamine system.

13:30-15:00 **Symposium: Molecular basis underlying social competence.** Chair: Hideaki Takeuchi. *Setouchi Hall, Room 1-2*

Regulatory mechanisms of social behavior in ants. Akiko Koto1, Naoto Motoyama1, Hiroki Tahara1, Masayuki Miura1, Laurent Keller2. 1) Dept. Genetics, Grad. Sch. Pharm. Sci., The Univ. Tokyo. 2) Dept. Ecology and Evolution, Univ. Lausanne. The social interaction with others has beneficial impact in various animals. Animals develop the flexible strategies to respond their social environment to maximize their fitness and health. By using social insects, in particular ants, we aim to understand the evolutionary origins of neural mechanisms that regulate social behaviors. For this, we focused on the physiological function of oxytocin/vasopressin-like peptides. Oxytocin/vasopressin-like peptides are neurohypophysial hormones composed of 9 amino acids, and evolutionarily conserved among wide range of animals, from worms to humans. Recent studies suggest that it functions to regulate social behavior in various animals. However the evolutionary origin of their molecular function is still unrevealed and we aim to study the neuronal function of their homologous nonapeptide, inotocin in ants. Ants exhibit sophisticated social organization with reproductive castes. Ant colony is composed from queens, males, and non-reproductive caste, workers. Workers show the division of labor, that is, each worker specializes in one job such as foraging, nurturing or nest construction. To understand the molecular function of inotocin signaling, we firstly performed the expression of analysis of inotocin and its receptor and found that inotocin and its receptor expression is higher in workers than males or queens. Inotocin expression is highest in the brain similar with oxytocin peptide. About the inotocin receptor, its expression was highest in the abdomen, but also detected in the head and thorax. From its expression, we hypothesized that inotoin signaling has a specific role in worker castes. To understand its molecular function, we are trying to develop the pharmacological and genetic strategies to manipulate inotocin signaling pathway and investigating the physiological function of inotocin signaling together with the behavior tracking system.

The Neurobiology of Social Bonding and Empathy-Related Behaviors in Monogamous Prairie Voles. Larry J. Young. Conte Center for Oxytocin and Social Cognition, Department of Psychiatry, Emory University, Atlanta GA, USA. The monogamous prairie vole provides an opportunity to examine the neural and genetic mechanisms underlying complex social behaviors, including social bonding and empathy-related behaviors. Oxytocin receptor (OXTR) signaling in the nucleus accumbens (NAcc) and prefrontal cortex (PFC) is critical for pair bond formation between mates. Diversity in expression patterns within the

brain contribute to diversity in social behaviors across and within species. In prairie voles, oxytocin links the neural encoding of the social signature of the partner with the rewarding aspects of mating through interactions with dopamine and by coordinating communication across a neural network linking social information with reward. Genetic polymorphisms robustly predict natural variation in OXTR expression in the striatum, which predict pair bonding behavior and resilience to neonatal social neglect. We have also explored the capacity of prairie vole to display empathy-like behavior, specifically consoling. Prairie voles increase their partner-directed grooming toward mates that have experienced an unobserved stressor. This consoling response is abolished blocking OXTR antagonist into the anterior cingulate cortex, a region involved in human empathy. There are many parallels between these observations in voles and the reported effects of oxytocin (OT) on human social cognition. In fact, the OT system is a leading candidate for treating social deficits in autism. However, OT does not efficiently penetrate the blood brain barrier. Using the prairie vole model, we have identified a pharmacological approach for evoking endogenous oxytocin release to enhance social cognition. Melanocortin agonists stimulate local dendritic OT release, thereby potentiating distal axonal release following physiological challenges. Peripherally administered melanotan II (MTII) efficiently enhances social bonding in voles. MTII robustly activates Fos expression in the NAcc and PFC, but only in the context of a social encounter. This social enhancement of NAcc and PFC activation by MTII is abolished by co-administration of an OT antagonist. Thus, MTII potentiates OT-dependent reward circuitry activation in the context of social interaction. We propose that pharmacology evoking endogenous OT release may be useful as an adjunct to behavior therapies for improving social cognition in autism.

Analysis of molecular basis underlying decision making according to social familiarity in small fish, medaka. Saori Yokoi1, Satoshi Ansai2, Yasuhiro Kamei1, Masato Kinoshita3, Yoshihito Taniguchi4, Larry J. Young5, Teruhiro Okuyama6, Takeo Kubo7, Kiyoshi Naruse1, Hideaki Takeuchi8. 1 National Institute for Basic Biology, Okazaki, Japan, 2 National Institute of Genetics, Mishima, Japan, 4 Division of Applied Biosciences, Graduate School of Agriculture, Kyoto University, Japan, 4 Department of Public Health and Preventive Medicine and, School of Medicine, Kyorin University, Japan, 5 Yerkes National Primate Research Center, Emory University, USA, 6MIT, USA, 7Department of Biological Sciences, Graduate School of Science, The University of Tokyo, Japan, 8 Graduate School of National Science Technology, Okayama University, Japan. Some social animals can recognize socially-familiarized conspecific individuals (social recognition) and familiarity affects their behavior, which may be important for social adaptation. Disorders in human brain function for this system are assumed to cause mental illnesses, such as autism, and great attention has recently been paid to the underlying neural/molecular mechanisms of these disorders. Oxytocin (OT) is considered to be involved in social recognition and social behavior in rodents and humans. For example, social familiarization (repeated encounters) decreases approach behaviors of male wild-type mice toward unfamiliar females, but not OT KO males. Thus, the OT KO males are thought to have defects in social recognition (social amnesia). In this study, we investigated social behaviors of individual medaka fish, which is a model organism commonly used for molecular genetics, toward group-reared fish (defined as familiar fish) in the same tank and toward unfamiliar conspecifics reared in a different tank. Wild-type males exhibit mating behaviors, irrespective of social familiarity. In contrast, we found that social familiarity strongly affects male social behaviors (e.g., courtship, aggressive, and mate-guarding behaviors) in isotocin-related gene mutants. Isotocin (IT) is a fish homologue of OT. This result suggested that IT-related gene mutants lost social motivation toward conspecifics. In some fish, imprinting affects the social preferences of the juvenile fish based on the traits of their parents that care for them during the early development period. Next, to examine whether or not imprinting mediates social

recognition of mutants for IT mutants, we investigated whether social familiarization (rearing in the same tank only as adults) could recover the lost of social motivation in the mutants toward unfamiliar fish.

Endocrine and mutual gazing regulate human-dog reciprocal communication. Miho Nagasawa1,2, Maki Katayama2, Shiori En2, Tatsushi Onaka1, Yasuo Sakuma3, Kazutaka Mogi2, Takefumi Kikusui2. 1 Jichi Medical University, 2 Azabu University, 3 University of Tokyo Health Sciences. Animals has developed empathy-related neural and behavioral systems, in which for example, weak and helpless member of individuals are protected and nurtured by other group members. This phenomenon is clearly observed in mother-infant relationship, such as bonding. Neurochemically, oxytocin in the neural system plays a pivotal role in forming mother-infant bonding in both sides, and there is a positive loop of attachment-parenting behavior via the oxytocin system in the infant-mother dyad. Humans form emotional bonds as we gaze into each other's eyes, and we discovered that such gaze-mediated bonding also exists between human and dogs, our closest animal companions. Mutual gazing increased oxytocin levels in both human and dogs. Administration of oxytocin increased gazing in dogs, and this behavioral change was transferred to their owners; increase oxytocin levels in humans. Mutual gazing may also relate to emotional contagion between human and dogs. Emotional contagion is known to be more effective in a close relationship, such as a bonding dyad. We investigated whether emotional contagion exists between human and dogs by measuring the heart rate variability. The results suggest that the duration the dogs gazing at their owners correlated with the correlation coefficient of the heart rate variability between the dogs and their owners. Other than humans, only dogs can convey emotions and form bonds by mutual gazing. This similar social attachment in both human and dogs might be a clue to elucidate the origin of empathy.

16:05-17:00 **Oral Presentations: Session 1 (8 minutes talk; 3 minutes Q&A).** Chair: Nii Addy. *Setouchi Hall, Room 1-2*

Evaluating photoperiodic effects on the serotonergic system during a sensitive developmental period. Justin K. Siemann1, Noah Green1 and Douglas G. McMahon1. Vanderbilt University1, Nashville, TN USA. Early life experiences during critical developmental time frames such as gestation and postnatal periods have been linked to increased risk for neurodevelopmental disorders later in life. Studies have shown seasonally varying risks for mood disorders with higher rates occurring during the fall or winter months when daylight is lowest in the year. The serotonergic system is known to be impacted by the duration of light exposure (i.e. photoperiod) and has been implicated in mood disorders, providing a promising new area of research. Thus, evaluating the mechanisms underlying the interaction between photoperiod and this system may provide understanding that is critical for developing insights into the etiology and novel treatment options. Recently, our lab has shown that mice exposed during development to long summer-like photoperiods of 16 hours of light and 8 hours of darkness each day (LD 16:8) demonstrate a greater neuronal firing rate of dorsal raphe serotonin neurons in isolated brain slices and higher levels of monoamines (i.e. serotonin and norepinephrine) in the midbrain along with more anxiolytic and anti-depressive behavioral effects compared to animals exposed to short winter-like LD 8:16 photoperiods. Based on these prior findings that used a developmental photoperiod from E0 to P30, we have now focused on when these photoperiod changes occur in development (i.e. a sensitive period), resulting in lasting changes in the serotonergic system. Specifically, we found that when animals were exposed only prenatally (E0-P0) to long photoperiods and then switched to a short photoperiod at birth, the average firing rate of dorsal raphe serotonin neurons measured in adulthood (P50-P90; 1.18 ± 0.076 Hz) resembled the firing rate for animals which continued to develop under a long photoperiod (1.24 ± 0.084 Hz). Interestingly, raphe neurons from animals that were prenatally exposed to a short photoperiod and then

switched to a long photoperiod at birth, displayed an intermediate firing rate (0.99 ± 0.083 Hz) compared to those that were continuously exposed to either a long (1.24 ± 0.084 Hz) or short photoperiod (0.69 ± 0.024 Hz) throughout development. Continuing with this photoperiod paradigm, we currently are determining the effects of photoperiod on prenatal and perinatal development by evaluating monoamine concentrations and behaviors relevant to anxiety and depression in adulthood. These findings demonstrate that photoperiodic programing of serotonin neurons can occur in utero, long photoperiods may be serving as an active agent and affecting the serotonergic system perinatally, and exposure to short photoperiods in utero may extend the critical period into the perinatal period. By evaluating a developmental sensitive period for the effects of photoperiod on the serotonin system, this may provide novel insights into therapeutic treatments for mood related disorders.

Reducing FKBP5 expression in the ventral hippocampus produces a PTSD-like phenotype without affecting anxiety or depressive-like behaviors. Marangelie Criado-Marrero1,2, Benjamín López-Torres1, César Torres Gutiérrez1, Anixa Hernández1, María Colón1, Ramón Misla David1, Chad A. Dickey2, James T. Porter1. 1Ponce Health Sciences University, Ponce, P.R.; 2University of South Florida, Tampa, FL. Despite the association of FK506 binding protein 5 (FKBP5) polymorphisms with post-traumatic stress disorder (PTSD), the mechanisms by which FKBP5 dysfunction can produce PTSD-like phenotypes is still unknown. Patients with PTSD have shown reduced FKBP5 gene expression in blood and impaired hippocampal activity. Since the hippocampus is sensitive to stress and FKBP5 impedes glucocorticoid receptor signaling, reduced FKBP5 expression could facilitate the formation of long-lasting traumatic memories by allowing enhanced glucocorticoid receptor activity. Thereby, we hypothesized that the uncontrolled fear response after trauma may be due to hippocampal malfunction as a consequence of low levels of FKBP5. To test this, we examine the baseline FKBP5 protein levels in ventral hippocampus (VH) and blood in adult male rats, and then compare expression changes after fear conditioning and extinction. We found that FKBP5 was reduced in VH after fear conditioning and this protein reduction was negative correlated with conditioned fear expression suggesting that less expression of FKBP5 protein in VH might facilitate the acquisition of conditioned fear. Next, we assessed whether reducing FKBP5 protein in VH is sufficient to alter fear conditioning. We infused into the rat's brain a FKBP5 shRNA plasmid to reduce FKBP5 protein and waited 5 days before exposing to behavioral test. By lowering FKBP5 in VH, our rats showed a PTSD-like phenotype with enhanced fear acquisition during fear conditioning and fear extinction recall. We further observed that the c-fos expression in VH was significantly increased in rats infused with FKBP5-shRNA compared to control infused rats indicating that reducing FKBP5 increases VH activity. To eliminate the possibility that reducing FKBP5 in VH enhances freezing behavior during auditory fear conditioning by reducing locomotion or increasing anxiety-like or depression-like behaviors, we exposed separate groups to open field, elevated zero maze, and force swimming tests five days after infusion of FKBP5-shRNA plasmid in VH. Our results confirmed that reducing VH FKBP5 affects fear conditioning and extinction without affecting locomotion, anxiety-like, or depression-like behaviors. Our findings extend other studies showing changes in VH FKBP5 activity as we directly demonstrate that modulating FKBP5 in this structure affects fear learning, as it may be also happening in patients with PTSD. Thus, future studies should be directed to describe the molecular mechanism by which FKBP5 modulates fear expression in the VH. This project is supported by the RCMI Behavioral and Molecular Biology Core Labs (Grant 8G12MD007579), R15 MH101700, RISE Program (Grant R25GM082406), and Diversity Supplement NS073899 (Dickey/Criado-Marrero) from the National Institutes of Health.

Daily oxytocin treatment during abstinence from methamphetamine self-administration in male and female rats: Effects on relapse to drug-seeking, social interaction and anxiety. Nicholas Everett1, Sarah Baracz2, Jennifer Cornish1. 1Macquarie University, NSW, Australia 2University of Sydney, NSW, Australia. Methamphetamine (METH) is a highly addictive psychostimulant, abuse of which is characterised by long term psychiatric and social consequences, and chronic relapse to drug-taking. Acute administration of the neuropeptide oxytocin has shown great potential as an anti-craving treatment for METH dependence in rodent models of addiction, and has been shown to promote pro-social behaviours, and reduce anxiety in healthy rats. However, the effects of repeated oxytocin therapy in METH-experienced rats are not known. This is the first study to examine the outcomes of repeated oxytocin treatment during abstinence from methamphetamine self-administration on relapse propensity, anxiety, and social deficits, across both sexes. Male and female Sprague-Dawley rats with implanted jugular vein catheters were trained to self-administer METH (0.1mg/kg/infusion) under a fixed-ratio 1 schedule of reinforcement for 2 hours per daily session. After 12 sessions, rats were allocated to 6-hour or 2-hour sessions for another 11 sessions, and then underwent drug abstinence. On day 2 of abstinence, rats underwent cue-induced reinstatement, and then were tested on measures of anxiety and social interaction. Following this, rats received daily i.p. injections of oxytocin (1mg/kg) or saline for 15 days. Three days after the last oxytocin or saline injection, rats underwent the same battery of anxiety and social tests. On day 30 of abstinence, rats underwent another cue-induced reinstatement test. After a week of behavioural extinction training, all rats then underwent reinstatement tests following injection with the anxiogenic drug yohimbine (0.625 and 1.25mg/kg i.p.) and then METH (0.3 and 1.0 mg/kg i.p.). Escalated daily intake (6 hour) of METH resulted in the incubation of METH-craving from day 2 to day 30 of abstinence, as well as augmented yohimbine and METH primed reinstatement to drug seeking. Importantly, rats which received 15 days of oxytocin injections during abstinence had partially attenuated reinstatement to drug-seeking following METH administration, and following the presentation of drug-associated cues. Preliminary analyses also point to sex-dependent interactions of METH exposure and oxytocin treatment on anxiety and social behaviours. Overall, these findings demonstrate that chronic therapy with oxytocin in abstinent METH users may partially attenuate the incubation of drug cravings, and remediate METH-induced behavioural changes, providing further support for oxytocin as a pharmacotherapy for METH dependence.

Nucleus incertus and its neuropeptide relaxin-3 influence perforant path-dentate gyrus synaptic plasticity in rats. Mohsen Nategh1, Fereshteh Motamedi1. 1Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Involvement of brainstem nucleus incertus (NI) in hippocampal theta rhythm suggests that this structure might play a role in hippocampal plasticity as well as learning and memory. We have previously shown that NI inactivation did not affect short-term plasticity in perforant path-dentate gyrus, but caused a weak induction of long-term potentiation (LTP) compared to the control group. NI inactivation in the aftermath of induced LTP did not alter synaptic response. In the present study, we aimed to address if relaxin-3, the major neuropeptide of NI is involved in hippocampal short-term and/or long-term synaptic plasticity in behaving rats. Using an assembled cannula-electrode, exogenous relaxin-3, the major neuropeptide of NI, was administered directly into DG to mimic NI activity. In freely moving rats, perforant path-dentate gyrus short-term and long-term synaptic plasticity were studied respectively by paired-pulse and high-frequency stimulations (HFS) after relaxin-3 injection. Post-HFS synaptic activity was recorded for 2 hours, and then again at 24hr. It was found that direct relaxin-3 injection into DG did not alter basic synaptic response or LTP induction, but caused facilitation in normally inhibitory paired-pulse responses of medial perforant-DG. Contrary to NI inactivation which blocks all NI output, relaxin-3 imitates direct activity of NI on DG. Regarding the

findings, it appears that NI does not influence hippocampal plasticity only through direct innervation. Moreover, it is anticipated that NI preferentially innervate inhibitory interneurons over granule cells in the DG circuitry. Further studies should address direct and indirect paths through which NI might influence hippocampal plasticity. Acknowledgement: This work was supported by a grant from Shahid Beheshti University of Medical Sciences.

Reevaluation of rodent compulsive-like, depression-like, and anxiety-like behavioral tests in a non-induced mouse model of OCD. Abel Bult-Ito, University of Alaska Fairbanks. Nest-building and marble burying behaviors have been established as tests for compulsive-like behaviors, while the forced swim test and the tail suspension test are thought to measure depression-like behavior. The open field and elevated plus maze tests are used to test for anxiety-like behavior, while the marble burying test is also used to test for anxiety. These tests have been used in our non-induced mouse model of obsessive-compulsive disorder (OCD), which consists of two independently maintained mouse strains selected for using large amounts of cotton for a nest. These compulsive-like mice are also compulsive diggers in the marble burying test compared to two non-compulsive-like mouse strains selected for building small nests. We have found that the standard 20-min marble burying test was too long for our compulsive-like mice, because they started reburying the marbles after about 10 minutes into the test, leading to underestimation of the level of digging. Although the compulsive-like mice showed more depression-like behavior in the first minute of the forced swim test than the non-compulsive mice, this difference disappeared for the full 6-min test, primarily because the compulsive-like mice had very little buoyancy once their fur absorbed water. In contrast, the tail suspension test showed the compulsive-like mice to be less depression-like than the non-compulsive-like mice. In the open field test, anxiety-like behavior or locomotor activity were not correlated with the level of compulsiveness. In the elevated plus maze, compulsive-like mice were less anxiety-like than the non-compulsive-like mice. The results of these anxiety test suggest that the marble burying test was less likely to measure anxiety-like behavior and more likely to measure compulsive-like behavior. Depression and anxiety are often comorbid with the OCD in humans, which contradicts our findings in our mouse model of OCD. The question is whether the tests used measure depression-like and anxiety-like behaviors that are equivalent to OCD patients, whether the test themselves do not measure what they have been thought to measure, or whether our mouse model of OCD is only relevant to OCD patients without comorbid depression and/or anxiety. This presentation hopes to shed some light on this question.

16:05-17:00 **Oral Presentations: Session 2 (8 minutes talk; 3 minutes Q&A).** Chair: Tiffany Donaldson. *Setouchi Hall, Room 6*

Interaction of chronic unpredictable stress and brain trauma on cognitive performance, depressive-like behaviors and immune markers. C. O. Bondi, L. Kutash, D. O'Neil, I. Marshall, J. P. Cheng, P. B. de la Tremblaye, A. E. Kline. Safar Ctr. for Resuscitation Res., John G. Rangos Research Center, Children's Hospital of Pittsburgh, Univ. of Pittsburgh, Pittsburgh, PA, USA. Traumatic brain injury (TBI) affects 2 million individuals in the United States each year, and many survivors endure long-lasting cognitive impairments associated with frontal lobe disturbances, while also being vulnerable to neuropsychiatric disorders. Clinical and preclinical research has highlighted the importance of chronic stress, particularly when presented in an unpredictable fashion, as a major risk factor for many psychopathological conditions. In the current study, we began to assess clinically-relevant cognitive-behavioral and anxiety-like dimensions sensitive to both TBI and chronic unpredictable stress (CUS). We hypothesized that moderate TBI produced by controlled cortical impact (CCI) injury, as well as CUS exposure will render

cognitive impairments in male rats in an attentional set-shifting test (AST), reduced sucrose preference and open field exploration, as well as blunted weight gain. Isoflurane-anesthetized adult male rats were subjected to a CCI (2.8 mm cortical tissue deformation at 4 m/sec) or sham injury over the right parietal cortex. Following surgery, rats were randomly assigned to receive CUS (21 days starting 5 days post-surgery) or 30 sec of handling (CTRL). Upon cessation of stress, rats were tested for perceived state of anxiety (open field test) and anhedonia (reduced preference of 1% sucrose-water versus regular water overnight). At 4 weeks post-surgery, rats were then tested on the AST, which involves a series of increasingly difficult discriminative tasks to obtain food reward. Results demonstrate that CUS exposure leads to a 5-10% weight gain reduction compared to CTRL group, yet the combination of TBI and CUS does not negatively impact center exploration in the open field, or sucrose preference (n=8-12/group). TBI and CUS rendered cognitive deficits when given alone, as expected, but not when given in combination, suggesting a resilience interaction. Ongoing directions include assessing serum levels of various immune markers such as IL-4, IL-6, IL-10, IL-12 and TNFα, as well as measuring protein levels in multiple discrete brain regions for markers relevant to neurotransmitter synthesis, release and reuptake. This ongoing project will provide novel outcomes pertaining to cognitive capability, as well as anxiety- and depressive-like symptoms following overlapping chronic stress exposure and the recovery phase of TBI.

Cortical-amygdala circuits for value-based decision making. Melissa Malvaez1, Christine Shieh1, Michael Murphy1, Venuz Y. Greenfield1, Harold G. Monbouquette3, and Kate M. Wassum1,2. 1. Dept. of Psychology, UCLA, Los Angeles, CA 90095. 2. Brain Research Institute, UCLA, Los Angeles, CA 90095, USA. 3. Dept. of Chemical Engineering, UCLA, Los Angeles, CA 90095, USA. The value of an anticipated reward is a major contributing factor in the decision to engage in actions towards its pursuit. Such value is dynamic, fluctuating based on one's current need state, and must be learned through relevant state experience (e.g., consumption of a food item while hungry). The basolateral amygdala (BLA) is required for this incentive learning process, but little is known about how it achieves this function within the broader reward-seeking circuitry and whether it also participates in the online use of reward value during decision making. Because the BLA is densely innervated by cortical glutamatergic projections, we hypothesized that glutamate released into the BLA would track changes in reward value important for value-guided reward seeking. To test this, we used electroenzymatic biosensors to make near-real time measurements of BLA glutamate concentration changes during incentive learning (experience with a food reward in novel hungry state) and a subsequent reward-seeking test. Transient elevations in BLA glutamate concentration were detected that tracked the incentive learning process. No such changes were detected in the absence of incentive learning when the food was experienced in a familiar state. BLA glutamate elevations were also detected immediately preceding bouts of subsequent reward-seeking activity, but only if rats had access to the current value of the food reward. Supporting these correlational data, inactivation of BLA NMDA glutamate receptors prevented incentive learning, while inactivation of either BLA AMPA or NMDA receptors attenuated the normal increase in reward seeking that would occur following a positive incentive learning opportunity. We next used designer receptor-mediated inactivation of specific glutamatergic cortical projections to the BLA to determine the afferent contributors to these input signals. Projections from the lateral orbitofrontal cortex (OFC) were found to be necessary for encoding a positive change in reward value, but not for later retrieval of this information for online decision making. Conversely, projections from the medial OFC were not required for incentive learning, but their inactivation did disrupt online reward-seeking activity. These data demonstrate that the BLA participates in both the encoding and retrieval reward value via input signals from the lateral and medial OFC, respectively. NRSA 1F32DA038942. TNDA 5T32DA024635. R01-DA035443.

TRPV1 receptor modulates different phases of conditioned fear learning. Ana Luisa Terzian; Leonardo BM Resstel. School of Medicine of Ribeirão Preto. University of São Paulo, Brazil. TRPV1 receptor (rTRPV1; transient receptor potential vanilloid type 1) is widely distributed in the central nervous system (CNS), on areas involved with modulation of emotional responses such as midbrain and prefrontal cortex. Pharmacological or genetic inhibition of this receptor reduces neuronal activity, resulting in decreased fear and anxiety levels. However, few studies investigated the role of rTRPV1 on different phases of acquired fear, which is highly related to species survival and several psychiatric disorders. Therefore, this study aimed to investigate the role of rTRPV1 in different phases of cued fear conditioned (CFC) in wild-type (WT) and rTRPV1 knockout mice (TRPV1-/-). Mice (WT or TRPV1-/-; C57bl/6 background; 8-12 weeks) were submitted to the 3-days CFC protocol. On the first day (d0), animals received foot-shock associated with an auditory cue in context A [5 shocks, 0,65mA, 1s; paired with a tone (30s, 1kHz, 70dB)]. Twenty-four hours later (d1), animals were placed in a different context B, where the auditory cue was presented without foot-shock. On the third day (d2), animals were submitted to the same conditions as in d1. The fear acquisition (d0), extinction (d1) and extinction learning (d2) were evaluated based on the level of freezing behavior. WT mice implanted with guide cannula into the medial prefrontal cortex received microinjection of TRPV1 antagonist 6-iodonordihydrocapsaicin (6-iodo; 3-10nmol/100nL) or vehicle. Microinjections were performed either pre-d1, post-d1, or pre-d2. On CFC protocol, the cued fear acquisition was similar for all groups tested. Nonetheless, on the following days (d1-d2) TRPV1-/- showed reduced freezing behavior, resulting in improved extinction learning when compared to control. TRPV1 antagonist 6-iodo reduced fear expression in d2, independent of injection time, suggesting a long-lasting effect after receptor blockade. In conclusion, our results suggest rTRPV1 involvement in the modulation of learned behaviors with emotional content, indicating a prospective treatment for several psychiatric disorders. Financial support: FAPESP, CAPES, CNPq, IBRO, IBNS.

Sex differences in behavioral and cellular activational responses to central CRF administration in male and female rats. Stefanie M Klampfl, Yi Yang, Judy Chang, Victor Viau. The University of British Columbia, Vancouver, Canada V6T 1Z3. The incidence of anxiety and depression is higher in women compared to men. Stress is one of the leading causes of these psychopathologies, frequently accompanied by maladaptive behavioral and neuroendocrine coping responses. As these responses are mainly orchestrated by the brain corticotropin-releasing factor (CRF) system, CRF and its family members have emerged as key candidates involved in the development of stress-related disorders. However, how the CRF system contributes to sex differences in coping responses remains largely unclear. Here we compared home cage behaviors and patterns of cellular (Fos) activation following intracerebroventricular administration of exogenous CRF in adult male and female rats. Compared to males, females showed faster increases in self-grooming and greater latencies to return to non-active behaviors after CRF administration. CRF-induced decreases in locomotion were entirely restricted to females, as no such effect occurred in males. Furthermore, we found marked sex differences in regional patterns and numbers of cells recruited to show Fos protein in response to exogenous CRF. Our analysis so far indicates that CRF increased Fos in cortical, septal, hypothalamic and thalamic nuclei in males while in females only aspects of the extended amygdala were activated. These findings indicate a broader capacity for males to react to CRF receptor activation within brain regions implicated in cognitive/affective processes, whereas responses in females appear to be restricted to regions involved in emotional and autonomic regulation. Finally, sex differences in behavioral and activational responses did not correlate with plasma concentrations of estradiol, progesterone and testosterone, to suggest that sex differences in CRF responses occur independent of variations in gonadal status. In conclusion, sex differences in the

behavioral repertoire and patterns of cellular activation evoked by exogenous CRF predict underlying sex differences in CRF receptor function and circuit requirements for stress coping in males and females. This study was supported by the German Research Foundation (SMK) and by the Canadian Institutes of Health Research (VV).

17:05-18:00 **Oral Presentations: Session 3 (8 minutes talk; 3 minutes Q&A).** Chair: Farida Sohrabji. *Setouchi Hall, Room 1-2*

A role for the anterior cingulate cortex in the encoding and recall of contextual defensive responses to predatory threats. De Lima, M.A.X.; Canteras, N.S. Department of Anatomy, Institute of Biomedical Sciences – University of São Paulo. The hypothalamic predator responsive circuit is known to influence contextual memory through its projections to the ventral part of the anteromedial thalamic nucleus (AMv). Recent studies from our laboratory indicates that the AMv influences the acquisition, but not the expression, of contextual conditioned defensive reactions to predatory threats. The AMv is known to provide strong projections to a specific cortical circuit, where the anterior cingulate cortex (ACA) occupies a central position. The ACA is connected to areas known to participate in the mnemonic processing related to the fear memory. In the present study, we investigated how the ACA influences different phases of the mnemonic processing (i.e., acquisition and recall). To this end, we expressed hM4D (Gi) receptors in the ACA of mice by using adeno-associated virus, and silenced this area by injecting clozapine n-oxide (CNO) during the encoding or recall window of the predator exposure test. The virus infection and the CNO injection did not alter the innate responses during cat exposure. Inhibition of the ACA immediately both before the cat exposure, or the context exposure, disrupted the learned defensive responses typically displayed by the control groups, thus suggesting the ACA participation in both the acquisition and recall of predator fear memories. We have further analyzed Fos expression the dorsal periaqueductal grey (dPAG), and found that inactivation of the ACA during the acquisition or expression phases dropped down dPAG Fos expression in animals exposed to the predatory context. As future steps, by using optogenetic inhibition of different sets of ACA projections, we intend to investigate whether there is a differential participation of different sets of ACA projections in the acquisition or expression of contextual fear responses. FAPESP grant support # 2014/05432-9 and #2016/10389-0.

D2L receptor-expressing striatal neurons control visual discrimination learning in a touchscreen operant system. Takatoshi Hikida1, Makiko Morita1, Tom Macpherson1. 1Medical Innovation Center, Kyoto University Graduate School of Medicine. Visual discrimination learning requires perceptual learning and memory processing via corticostriatothalamic circuitry. Abnormalities in visual discrimination learning have been shown in patients with various psychiatric disorders such as schizophrenia, autism and Altzheimer's disease. Considerable evidence has demonstrated a critical role for the basal ganglia in visual discrimination learning. These processes are guided by the activity of two discrete neuron types, dopamine D1- or D2L-receptor expressing medium spiny neurons (D1-/D2-MSNs) in the basal ganglia circuit. We used a reversible neurotransmission technique (D1-/D2-RNB; Hikida et al., 2010) to examine the role of D1- and D2-MSNs in visual discrimination learning in a touchscreen operant system. We demonstrated that D1- and D2-RNB have no effect on an operant conditioning task, but that D2-RNB impairs visual discrimination learning. Additionally, global knockout of the dopamine D2L receptor isoform produced a similar behavioral phenotype to D2-RNB mice. These results suggest that D2L receptors and D2-MSNs have a critical role in basal ganglia circuit mechanisms for visual discrimination learning. Funding: KAKENHI 15H04275, 16K14579, 16H06568.

BIN1 risk factor-based transgenic mice as a model of specific early phenotypes of presymptomatic Alzheimer disease including recognition memory impairments. Simonneau M1, 2, Daudin R1,2, Marechal D3, Abe Y4, Loe-Mie Y 1, Potier B1,2, Dutar P1,2, Viard, J 1, Lepagnol-Bestel A.M 1, Birling MC3, Pavlovic G3, Herault Y3, & Ciobanu L4. 1LAC, UMR CNRS-ENS Paris-Saclay, Université Paris-Saclay, 91405 Orsay, France. 2Centre Psychiatrie & Neurosciences, INSERM U894, 75014 Paris, France. 3 Institut de Génétique et de Biologie Moléculaire et Cellulaire, 67404 Illkirch, France. 4NeuroSpin, CEA Saclay-Center, Université Paris-Saclay, Gif-sur-Yvette, France. Late-onset Alzheimer Disease (LOAD) is the most common form of dementia and one of the most challenging diseases of modern society. A selective impairment of episodic memory before the diagnosis of LOAD has been consistently reported, pointing that early changes in the hippocampal complex play an important role in the memory deficits in preclinical Alzheimer's disease. The entorhinal cortex (EC) is a critical component of our episodic memory system, with tau abnormalities and tangle pathology very early in the course of the disease (Braak stage I) (Braak, H. & Braak, E. Acta Neuropathol. 1991). Lateral (LEC) and medial (MEC) portions of EC are respectively involved in object processing and non-spatial mnemonic functions whereas the MEC, which contains spatially tuned grid cells, have spatial mnemonic functions. New findings in preclinical LOAD patients indicated that it is the LEC, rather than the MEC that is most susceptible to tau pathology early in Alzheimer's disease, with spreading to the parietal cortex (Khan et al., Nature Neuroscience 2014). New susceptibility genes have been evidenced using LOAD Genome Wide Association Studies (Lambert et al., Nature Genetics, 2013) including BIN1 as the second most important risk locus for LOAD following apolipoprotein E (APOE). Here we report transgenic mice carrying a bacterial artificial chromosome containing the full human BIN1 gene in order to mimic expression changes of BIN1 found in patients. These mice display specific early impairment of entorhinal cortex-Dentate Gyrus synaptic plasticity in hippocampus, at 3-months of age. We found abnormal object recognition followed by impaired pattern recognition. In contrast, spatial memory analyzed by Morris Water Maze was not affected. These phenotypes involve changes of BIN1/TIAM/RAC1 pathway in dendritic spines of dorsal Dentate Gyrus. Altogether, these changes are in agreement with a specific impairment of LEC-Dentate Gyrus pathway. Furthermore, MRI-DTI (17.2 Tesla) studies evidenced changes in fractional anisotropy (FA) and mean diffusivity (MD), specifically in EC and related hippocampal sub-regions at 3-months with an extension to cortex at 15-months, indicating a progression of demyelination and inflammation in this novel LOAD model. As no proven effective treatment is available, this work points to molecular mechanisms that can be targeted for therapeutic purposes. Funded in part by European FP7-Health AgedBrainSYSBIO.

Intrauterine undernourishment break down the mirnome that controls proliferation, development and migration of the oligodendrocyte. Ramírez-Orozco, Paulina[1]; Guadarrama-Olmos, José Carlos[2]; Lara-Lozano, Manuel [2]; García-Vázquez, Raúl[3], Jiménez, Ismael[2] and González-Barrios, Juan Antonio[4]
[1] Escuela de Dietética y Nutrición del ISSSTE, [2] Departamento de Fisiología, Biofísica y Neurosciencias del CINVESTAV, [3] Departamento de Ciencias Genómicas de la Universidad Autónoma de la Ciudad de México, [4]Laboratorio de Medicina Genómica, Hospital Regional "1° de Octubre", ISSSTE. Nutritional deficiency during pregnancy leads to intra-uterine growth deficiency, affecting the development of fetal cells especially those of the central nervous system. Myelination defect is a common feature of fetal growth restriction in maternal undernourishment, due to a deficit of myelination and a disturbance of oligodendroglial maturation induced by: arrested maturation of the oligodendroglial lineage, increased apoptosis of immature oligodendrocytes, and decreased proliferation of oligodendrocyte progenitors. However, the molecular mechanisms that underlie these phenotypes remain unknown. The mirnome and chemotactic transcriptome of white and grey matter of male pups with intrauterine undernourishment

was analysed by qPCR using TLDA technology and individual Taqman probes, the differences were compared to intrauterine well nourished male pups. We found that intrauterine undernourishment decreased the expression of: rno-miR-31a-3p (p = 0.043), rno-miR-30d-3p (p = 0.04), rno-miR-27a-5p (p = 0.04), rno-miR-34b-3p (p = 0.036), rno-miR-34c-3p (p = 0.037), rno-miR-219a-3p (p = 0.033), rno-miR-224 (p = 0.0224) and rno-miR-449a-5p (p = 0.006) and increased rno-miR-1274a (p = 0.008) and rno-miR-10a# (p = 0.005) in the white matter, these changes correlate with the gene transcription increase of: IGF-1, BDNF, CXCL13, CXCL12, CCL4, CXCR4, CCR2, NOS1, NOS3, SOD1, SOD3 and decreased of the CXCR5, NOS2 and CCR8 transcription. While in the gray matter the transcription of: GDNF, CCR8, SOD3, NOS2 and SOD3, increased, and the transcription of: NFκB, NGF, IGF1, FGF2, VEGF, CCL4, CXCL13, CCR2, CXCL3, CXCL2, CXCR5, SOD1 and SOD2 decreased. These results show that the mirnome dysregulation is the main target of intrauterine undernourishment causing the development of myelination defects. This study highlights the role of mirnome in the regulation of proliferation, development and chemotaxis of the oligodendrocytes.

Individual recognition and face inversion effect in medaka fish (Oryzias latipes). Mu-Yun Wang1, 2 & Hideaki Takeuchi1, 2. 1Department of Biological Sciences, Graduate School of Science, The University of Tokyo, Tokyo, Japan. 2The Graduate School of Natural Science and Technology, Okayama University, Okayama, Japan. Individual recognition (IR) is essential for maintaining various social interactions in a group, and face recognition is one of the most specialised cognitive abilities in IR. We used both a mating preference system and an electric shock conditioning experiment to test IR ability in medaka, and found that signals near the face are important. Medaka were better at identifying different conspecific faces compared to non-face shapes, and required more time to discriminate vertically inverted faces, but not horizontally shifted faces. When the non-face shapes were inverted vertically, neither decision time nor accuracy was increased. Extra patterns added to the face also did not influence medaka IR. These findings suggest that the process of face recognition may differ from that of other objects. Despite the phylogenetic differences between mammals and medaka, the ability to recognize conspecific faces and the face-inversion effect are similar, but the mechanisms and neurological bases may be distinct. MYW is supported by FY2013 JSPS Postdoctoral Fellowship for Foreign Researchers and JSPS Grant-in-Aid number 25-03074. HT is supported by JSPS KAKENHI Grant Numbers 26290003, the Grant-in-Aid for Scientific Research on Innovative Areas “Memory dynamism” (26115508) from the Ministry of Education, Culture, Sports, Science, and Technology; Brain Science Foundation; and Yamada Science Foundation.

17:05-18:00 **Oral Presentations: Session 4 (8 minutes talk; 3 minutes Q&A).** Chair: Kim Gerecke. *Setouchi Hall, Room 6*

Oxytocinergic projections facilitate male sexual behavior via the spinal gastrin-releasing peptide system. Oxytocinergic projections facilitate male sexual behavior via the spinal gastrin-releasing peptide system. Takumi Oti1, Keita Satoh1, Keiko Takanami1, Junta Nagafuchi1, John F. Morris2, Tatsuya Sakamoto1, Hirotaka Sakamoto1. 1Ushimado Marine Institute (UMI), Okayama Univ, Okayama, Japan, 2Dept Physiology, Anatomy, and Genetics, Le Gros Clark Building, Univ Oxford, Oxford, UK. We previously demonstrated that the gastrin-releasing peptide (GRP) system in the lumbar spinal cord mediates spinal centers promoting penile reflexes in rats. These GRP expressing neurons in the upper lumbar spinal cord (L3–L4 level) project to the lower lumbosacral spinal cord (L5–S1 level), innervating regions known to control erection and ejaculation. A group of oxytocin (OXT) neurons situated in the parvocellular part of the paraventricular nucleus (PVN) and projecting to the spinal cord might control penile reflexes. Therefore, the hypothesis that OXT, which is transported by long descending PVN-spinal pathways,

activates proerectile spinal centers has been proposed. However, the direct linkage of the neural circuit between the hypothalamic PVN and penile innervation remains uncharacterized. Hence, the purpose of this study is to reveal the function of OXT in the brain-spinal cord neural network regulating male sexual function. First, we found that the axonal distribution of OXT in the lumbar spinal cord exhibits a male-dominant sexual dimorphism in rats. Furthermore, OXT binding and expression of the specific OXT receptor were observed in the somata of spinal GRP neurons. Next, we studied the expression of phosphorylated extracellular signal-related kinase (pERK), a marker for neuronal activation, in the GRP neurons after sexual behavior. As a result, pERK induction in the GRP neurons appeared to be specifically associated with ejaculation. Subsequently, the local administration of OXT into the upper lumbar spinal cord at the location of the GRP neurons significantly increased pERK expression in GRP neurons, suggesting that secreted oxytocin in the lumbar spinal cord activates the GRP neurons during male sexual behavior. Moreover, intrathecal administration of the OXT receptor antagonist decreased the number of intromissions and most strikingly, decreased the number of ejaculations. Taken together, these results suggest that the hypothalamic OXT projections facilitate male sexual behavior via the GRP system in the lumbosacral spinal cord.

Impact of unhealthy diets on gut microbiome and behavior? studies in rats. Morris Margaret J1, Beilharz Jess1, Maniam Jayanthi1, Kaakoush Nadeem1. 1Medical Sciences, UNSW Sydney, NSW Australia 2052. A range of studies in animals and humans have demonstrated that exposure to diets rich in either fat and sugar, or sugar alone, can influence cognition. The hippocampus appears sensitive to dietary insult, specifically on hippocampal-dependent place recognition memory. People who report greater consumption of fats and sugars showed more marked loss of hippocampal volume. Our lab is interested in the relationship between diet-related changes in microbiota and behavioural deficits. While the Western diet is known to have detrimental effects on cognition and the gut microbiota, few studies have investigated how these may be related. Here, we examined whether probiotic administration could prevent diet-induced memory deficits. Rats were pre-exposed to vehicle, low or high doses of VSL#3 daily for 2 weeks by mouth before half were switched from chow to a cafeteria diet (Caf) for 25 days; VSL#3 treatment continued until sacrifice. Fecal DNA extraction was performed using the PowerFecal® DNA Isolation Kit. Caf rats were heavier with greater fat mass than those consuming chow, and VSL#3 had no impact on these measures. High dose VSL#3 prevented the diet-induced memory deficits on the hippocampal-dependent place task, but the probiotic led to deficits on the perirhinal-dependent object task, irrespective of diet or probiotic dose. No differences were observed in anxiety-like behaviour on the elevated plus maze. Gut microbial diversity was dramatically decreased by Caf diet and here, VSL#3 was able to increase the abundance of some taxa contained in the probiotic such as Streptococcus and Lactobacillus and also other taxa including Butyrivibrio, which were decreased by the Caf diet. In the hippocampus, the Caf diet increased expression of many genes related to neuroplasticity and serotonin receptor (5HT) 1A, which was normalised in Caf rats on high dose VSL#3. Neuroplasticity genes in the perirhinal cortex were also affected by Caf diet. Object memory performance was correlated with perirhinal 5HT2C expression. These results show that probiotics can be beneficial in situations of gut dysbiosis where memory deficits are evident but may be detrimental in healthy subjects.

5-HT1A and α2 adrenergic receptors modulate anxiety-like behavior and impulsivity in selective outbred Long-Evans rats. S. Tiffany Donaldson[1], Tim Niedzielak[2], Becky Ravenelle[3], Marie Joseph[1]. [1]Developmental and Brain Sciences, Department of Psychology, University of Massachusetts Boston, 100 Morrissey Boulevard, Boston, MA 02125, [2]Nova Southeastern University College of Osteopathic Medicine,

3301 College Avenue, Fort Lauderdale-Davie, FL 33314, [32]City University of New York, CUNY Neuroscience Collaborative, The Graduate Center, 365 Fifth Ave., New York, NY 10016. It is well established that pathological impulsivity is a psychological trait involved in many aspects of the drug addiction cycle. Anxiety also contributes to drug vulnerability in humans and rodents. We aimed to investigate whether rats selectively bred along a high anxiety domain that show amphetamine (AMPH) hyper-sensitivity would also display impulsivity in an operant task. High (HAn) and low anxious (LAn) 6th generation outbred male Long-Evans rats (N=16) were confirmed for anxiety level on the elevated plus maze (EPM) and tested for sensitivity to a low dose of AMPH (0.5 mg/kg, i.p.). Next, animals were exposed to a differential reinforcement of low rate of responding (DRL: 15s) operant schedule to assess impulsivity. 5-HT1A and α2 adrenergic receptor protein levels were measured across neural circuits implicated in anxiety and impulsivity. HAn animals displayed more anxiety-like behavior on the EPM and greater locomotor activity following AMPH. In the DRL, HAn rats attained fewer total rewards, had greater inter-response times when no reward was available, and greater burst ratios. HAn rats had a higher number of 5-HT1A receptor protein positive cells in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc). By contrast, levels of the α2 adrenergic receptor protein were lowered in mPFC and NAc for HAn rats; levels were increased in the locus coeruleus. Overall, these data suggest outbred male rats phenotyped as HAn show AMPH sensitivity that may be influenced by greater impulsivity, and that changes in corticolimbic levels of 5-HT1A and α2 adrenergic receptor proteins are associated with these psychological traits and psychostimulant vulnerability. Acknowledgements STD was supported by Award Number P20MD002290 from the National Institute on Minority Health and Health Disparities (Celia Moore, Ph.D., P.I.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Minority Health and Health Disparities or the National Institutes of Health.

Analysis of topographic memory and hippocampal neurogenesis in mice using the Hamlet Test. Tangui Maurice, Damien Gilabert, Mireille Rossel, Françoise Trousse, Lucie Crouzier. INSERM U1198, University of Montpellier, Montpellier, France. The Hamlet test is an novel fully automatized behavioral analysis appliance that provides a complex environment for testing topographic memory and spatio-temporal disorientation in mice. The apparatus mimics a small village with a central agora and streets expanding from it, leading to functionalized houses (Drink, Eat, Play, Run, Interact). Animals are habituated in groups of 6/8 individuals during 4 h a day, for several weeks. Memory can be tested by depriving mice from water (or food) during 20 h and testing, in a 10-min session, their ability to locate the Drink (or Eat) house. We analyzed the exploration pattern and topographical memory in different mouse strains (Swiss, C57BL/6, AKR) and gender. Habituated mice were compared to a control mice kept in housing cage. Significant differences in exploration patterns and street memorization were observed among strains and gender. The contribution of hippocampus, which plays a central role in spatial navigation, was investigated in C57BL/6 mice. Neurogenesis was analyzed in terms of proliferation, maturation and survival. BrdU immunohistochemistry was performed 24 hours and 2 weeks after BrdU injection to label newborn cells and cell survival, respectively. Increases in proliferative and survival markers (Ki67 and doublecortin) in the subgranular zone of the dentate gyrus, were measured after habituation. Using 3D fluorescence imaging, longer and highly branched doublecortin positive neurons were visualized. Neuroanatomical structures activated by habituation in the Hamlet were examined using ΔFosB immunochemistry. Expression levels of memory-related immediate early genes are currently analyzed. Animals administered with scopolamine (0.5-5 mg/kg SC) during habituation of before the probe test showed topographic memory impairment. In order to address the topographic disorientation in Alzheimer's disease, animals were trained during 2 weeks and then intracerebroventricularly injected with oligomeric Amyloid-ß25-35

peptide (9 nmol) or control peptide 3 days after training. When retested in the Hamlet after 7 days, Aß25-35-treated animals showed memory impairment. The data obtained so far suggest that orientation and memorization in the Hamlet test promotes maturation and differentiation of adult neural progenitors and boosts neuroplasticity. This test allows to study topographic memory in mice based on habituation to a complex environment and could offer an innovative tool to many research needs in various scientific fields. In particular, the Hamlet Test allows to specifically address topographic disorientation, an alert sign in Alzheimer's disease. Funding: This study was funded by a SATT AXLR (Montpellier, France) maturation grant.

Role of brain-derived neurotrophic factor (BDNF) in schizophrenia: studies in BDNF heterozygous and val66met polymorphic mice and rats. van den Buuse, Maarten1; Notaras, Michael J2; Jaehne, Emily1. (1) School of Psychology and Public Health, La Trobe University, Melbourne, Australia; (2) Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia. Post-mortem studies have shown significantly reduced brain-derived neurotrophic factor (BDNF) expression in the brain of schizophrenia patients. The BDNF val66met polymorphism has been associated with aspects of schizophrenia symptomology (Notaras et al., Neurosci Biobehav Rev, 2015). We used PPI, a behavioural endophenotype of schizophrenia, to further study the relationship between altered BDNF signalling and the illness. BDNF heterozygous mutant rats show a 50% decrease of mature BDNF protein levels in the brain, similar to deficits found in post-mortem studies. Baseline PPI, as well as disruption of PPI by the dopamine agonist, apomorphine, the NMDA receptor antagonist, MK-801, or selected serotonergic agents, was not different between the genotypes, potentially because of compensatory changes to the life-long reduction of BDNF expression in these animals. The BDNF val66met polymorphism results in reduced activity-dependent BDNF release rather than lower resting levels. Baseline PPI was significantly reduced in mice with the val/met genotype, but not the met/met genotype, compared to val/val controls. On the other hand, in previous experiments we found that environmental interventions such as chronic treatment with methamphetamine (Manning & van den Buuse, Front Cell Neurosci 2013) or cannabis (Klug & van den Buuse, Front Behav Neurosci 2013) unmask altered regulation of PPI in BDNF heterozygous mice compared to controls. BDNF val66met mice were therefore treated with corticosterone (CORT), to simulate stress, when they were 6-9 weeks of age and tested in adulthood. Mice with the val/met and met/met genotype were more sensitive than val/val mice to the effect of apomorphine, but not MK-801, to disrupt PPI. Chronic CORT treatment enhanced the effect of apomorphine in val/val mice, but had no further effect in the other genotypes. These results show that BDNF is involved in the regulation of PPI, an endophenotype of schizophrenia, but that its effect may be mediated by changes in activity-dependent release rather than reduced baseline protein levels or that additional environmental stress is required to unmask deficits in animal models.

18:30-20:30 **Poster Session 2.** *Setouchi Hall, Room 3-5*

1. **Regulation of rapid 17β-estradiol facilitated social recognition by MEK/ERK and PI3K/Akt cell signaling pathways in the dorsal hippocampi of female mice.** Sheppard PAS, Lumsden A, Ashley JS, Gumienny-Matsuo M, Choleris E. Department of Psychology and Neuroscience Program, University of Guelph, Guelph, ON, Canada. It is now established that estrogens can very rapidly affect learning and memory, occurring too quickly to be a result of classical gene-transcription mechanisms. In female mice, social recognition was facilitated within 40 minutes of systemic administration of 17β-estradiol (E2), estrogen receptor α (ERα) agonist PPT, or the G-protein coupled estrogen receptor (GPER1)

agonist G-1, but not the ERβ agonist DPN (Phan et al, 2011; 2012; Gabor et al, 2015). The dorsal hippocampus can mediate these effects as intrahippocampal administration of E2, PPT, or G-1 was sufficient to facilitate social recognition (Phan et al, 2015; Lymer et al, 2017). In addition, systemic administration of E2, PPT, or G-1 increases dendritic spine density in regions of the CA1 (Phan et al, 2011; 2012; Gabor et al, 2015). Estrogenic actions on cell-signaling cascades affecting dendritic spine dynamics and synaptic plasticity appear involved in estrogens' rapid learning effects. Two candidate cascades are the MEK/ERK and PI3K/Akt pathways. Blocking the phosphorylation of extracellular signal-regulated kinase (ERK) by mitogen activated protein kinase kinase (MEK) blocks estrogen facilitated increases in dendritic spine density *in vitro* (Sellers et al, 2015) and *in vivo* (Tuscher et al, 2016). Estradiol stimulates a rapid increase in post-synaptic density protein 95 (PSD-95) expression in an Akt-dependent manner (Akama & McEwen, 2003). Furthermore, estrogens require MEK/ERK and PI3K/Akt pathway activation to improve object and spatial memory (Fernandez et al, 2008; Fan et al, 2010; Fortress et al, 2013). Whether the MEK/ERK or PI3K/Akt pathways are involved in rapid estrogenic facilitation of social recognition in the hippocampus is unknown. Here we first determined the highest doses of MEK inhibitor U0126 and PI3K inhibitor LY294002 that do not block social recognition when infused in the dorsal hippocampus of ovariectomized female mice 15 min prior to testing. We then determined whether these doses of U0126 and LY294002 could prevent the enhancing effects of E2 (as in Phan et al., 2015) in a task where controls do not typically perform social recognition. These paradigms consist of habituation trails where two female conspecifics are presented and one test trial where one conspecific is novel and the other is familiar. The paradigms are completed within 40 minutes of E2 administration, thus enabling investigation of rapid effects of estrogens. MEK/ERK pathway activation was found to be necessary for E2 to rapidly facilitate social recognition as dose of 0.5μg/hemisphere of U0126 blocked the facilitation of social recognition E2. The PI3K/Akt pathway inhibition experiment is currently ongoing. These studies will provide a mechanism through which estrogens rapidly facilitate social recognition. Supported by NSERC.

2. **Ventral tegmental area L-type calcium channels mediates cue-seeking and dopamine release in the nucleus accumbens core during early withdrawal from cocaine**. EJ NUNES1, SM HUGHLEY1, KM SMALL1, RAJADHYAKSHA AM2, NA ADDY1,3. Exposure to drug associated cues facilitates drug-seeking behavior and promotes relapse in humans. In rodent models of drug addiction, presentation of drug paired cues increases burst firing in ventral tegmental area (VTA) DA neurons and phasic DA release in the nucleus accumbens core (NAc) that invigorates cue seeking for cocaine. L-type calcium channels (LTCCs) are expressed on VTA DA neurons and regulate burst firing. Moreover, VTA LTCCs are important for the reinforcing effects of cocaine and the synaptic plasticity associated with cocaine exposure. Yet, the role of VTA LTCCs on cue seeking for cocaine and phasic DA release in the NAc during forced abstinence are unknown. To address these questions, we first trained a cohort of male Sprague Dawley rats on 10 days of intravenous cocaine self-administration (0.5 mg/kg/infusion on a FR1 schedule), where active lever response resulted in intravenous cocaine delivery and the presentation of a compound cue (tone + light), while inactive lever responses had no programmed consequence. After the tenth day of cocaine self-administration, rats remained in their home cage with no access to cocaine or its cues for 10 days. Next, we asked if VTA LTCC blockade with isradipine (74pg and 223pg) in cocaine withdrawn rats would mediate cue-seeking during early withdrawal. We found that VTA LTCC blockade with isradipine (223 pg/side) reduced cue-induced cocaine-seeking on withdrawal day 10. When isradipine was given as a systemic injection (1.2mg/kg, I.P.) to cocaine

withdrawn rats, like VTA LTCC blockade, decreased cue-induced cocaine-seeking. In order to determine if VTA LTCC blockade was specific for cocaine reward, using the same procedure rats received a sucrose reward instead of cocaine. VTA LTCC blockade with isradipine (223 pg/side) did not alter cue-induced seeking for the natural reward sucrose. Using fast scan cyclic voltammetry (FSCV), we next sought to determine if VTA LTCCs mediates evoked DA release in NAc after cocaine self-administration and withdrawal. Blockade of VTA LTCCs with the same dose of isradipine (223pg) that decreased cue-seeking for cocaine during early withdrawal, increased evoked DA release in NAc across low and high frequency stimulation (5Hz or 60Hz; 24 pulses) of VTA. Similarly, when isradipine (1.2mg/kg I.P.) was administered systemically to cocaine withdraw rats there also was in increase in DA release in the NAc at low and high frequency stimulation of VTA. In contrast, blockade of VTA LTCCs with isradipine (223pg) in cocaine naïve rats or those that received sucrose reward instead of cocaine, did not alter phasic DA release in the NAc. Together, these results suggest a plasticity-dependent ability of VTA LTCCs to increase DA release in the NAc and modulate cue-induced cocaine seeking during early cocaine withdrawal. Future experiments will examine the role of VTA LTCCs on cue-evoked phasic DA release and D1 and D2 receptor mechanisms in NAc during cue-seeking for cocaine following forced abstinence.

3. **fMRI study of social exclusion and national identity using a cyberball paradigm**. Sujin Hong1, 2, Adam Moore3, Cyril Pernet 2, 4, Alexa M. Morcom3, Neil Roberts5, Agamemnon Krasoulis6, Laura Cram*1. 1Neuropolitics Research (NRlabs), School of Social and Political Science, University of Edinburgh, Edinburgh EH8 9LN, UK, 2Centre for Clinical Brain Sciences (CCBS), Neuroimaging Sciences, University of Edinburgh, 49 Little France Crescent, Edinburgh EH16 4SB, UK, 3Psychology, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK, 4Edinburgh Imaging, Neuroimaging Sciences, University of Edinburgh, Division of Clinical Neurosciences, Edinburgh EH4 2XU, UK, 5Clinical Research Imaging Centre (CRIC), Queens's Medical research Imaging (QMRI), University of Edinburgh, 49 Little France, Edinburgh EH16 4SA, UK, 6IPAB, School of Informatics, University of Edinburgh, 10 Crichton Street, Edinburgh EH8 9AB, UK. *Corresponding author. Shared neural correlates of ACC and PFC activation have suggested similarities between social and physical pain. A recent study showed that task related behavior in relation to in-group/out-group exclusion on the basis of gender also produced activation in vACC and vlPFC. Here we investigated social exclusion by national identity, where in-group and out-group members are distinguished by the Saltire flag (Scottish) and St George's cross flag (English), respectively. Healthy, right-handed, Scottish participants, aged between 18 and 45 (N=30), underwent blood oxygenation level-dependent (BOLD) contrast fMRI scanning. Participants played a computerised ball throwing game of cyberball with two other people shown on the computer screen during the fMRI scan, in the belief that they were playing with two people from different parts of the UK. A flag displayed in the top portion of the computer screen indicated the nationality of the two other players. In each condition, the participants received the ball 80% of the time for Inclusion, and received the ball 33% of the time for Exclusion. They were informed that they were taking part in a mental visualization exercise and should work hard to imagine the game as real. fMRI data analysis was performed using SPM12. Individual data in the first level analysis were modelled as 6 conditions using a GLM of the block design (2 conditions: Exclusion and inclusion × 3 Group identities: Scottish, English, and Control). The output was then entered into a repeated flexible factorial design in the 2nd level whole-brain analysis. Results showed a significant main effect of the Exclusion and Inclusion conditions, which produced activation in bilateral superior frontal areas, left calcarine and lingual

gyrus, extending to right fusiform gyrus, right precuneus gyrus, left superior parietal lobe, and left medial orbital frontal cortex (p(uncorrected)<.001 at voxel level, and multiple comparisons correction at the cluster level of p(FWE)<.05, k=50), whereas the main effect of group identities was not significant. Post-hoc t-test of Exclusion greater than Inclusion showed significant activation in medial OFC/vACC and Calcarine/lingual gyrus (p(uncorrected)<.001 at voxel-level with multiple comparisons correction at cluster-level of p(FWE)<.05, k=100). Involvement of vACC / OFC in social exclusion is consistent with previous studies and extends this research to show the neural response to social exclusion on account of nationality. This work was supported by the Economic and Social Research Council (ES/L003139/1).

4. **A bottom-up amygdala-cortical circuit controls cue-triggered reward-expectation.** Nina T. Lichtenberg1, Zachary T. Pennington1, Venuz Y. Greenfield1, Kate M. Wassum1,2. 1. Dept. of Psychology, UCLA, Los Angeles, CA 90095. 2. Brain Research Institute, UCLA, Los Angeles, CA 90095, USA. Appropriate decision making requires integrating what can be perceived in the environment (e.g., presence of stimuli or available actions) with information that is currently unobservable (e.g., knowledge of specific stimulus- or action-reward associations). The basolateral amygdala (BLA) and orbitofrontal cortex (OFC) are two identified key nodes in the circuit that support this expectation-guided reward seeking. The BLA and OFC share dense and reciprocal connections, suggesting that their interaction is needed for such behaviors. But understanding of the function of this circuit is limited by the fact that we do not know whether OFC-BLA circuitry contributes to the online control of decision making, the direction of information transfer, or whether any contribution of this circuit is via direct monosynaptic projections. Therefore, we used designer receptor-mediated inactivation of top-down OFC-BLA or bottom-up BLA-OFC monosynaptic projections to evaluate their respective contributions to expectation-guided behaviors. Inactivation of BLA terminals in the OFC, but not OFC terminals in the BLA, was found to disrupt the influence of cue-triggered reward expectations over both reward-seeking actions and conditioned goal-approach responding. Activity in these projections was not required when actions were guided by reward expectations generated based on known action-reward contingencies, or when rewards themselves, rather than expectations were present to direct responding. These demonstrate that BLA-OFC projections enable the cued recall of precise reward memories and the use of these expectations to guide and motivate specific action plans. Funding acknowledgements: NIH DA035443, T32 DA024635, UCLA Graduate Division.

5. **Retrograde Neurodegeneration of Substantia Nigra Projections to the Striatum following Long term survival after Ischemic Stroke**. Aditya Panta and Farida Sohrabji. College of Medicine, Neuroscience and Experimental Therapeutics. Texas A&M Health Science Center, College Station, TX 77843. Introduction: Stroke survivors suffer from long-term physical, cognitive and affective disabilities. These disabilities lower the quality of life, contribute to social isolation and anhedonia, and clinical disorders such as post-stroke depression (PSD), which disproportionately affects women. Preclinical studies show that lesions of the substantia nigra (par compacta) impair both motor performance and reward seeking behavior. Neurons from the SNc project to the striatum, a region that is significantly infarcted by middle cerebral artery occlusion (MCAo). Ischemia induced by MCAo leads to retrograde degeneration of the SNc pathway projecting to the striatum. Middle-aged Sprague-Dawley female rats (12 months old) were subjected to ischemic stroke using a silicon-coated nylon filament suture to occlude the middle cerebral artery (MCA) which was removed 75min after to allow for reperfusion.

After 14 weeks of survival, rats were again anesthetized and Fluorogold (Flg) was injected into the left and right striatum. Four days later, animals were overdosed with anesthetic, perfused with saline and formaldehyde and the brain removed for cryosectioning. In three sections per animal, Flg-labeled cells in the SNc were counted on both hemispheres, using fluorescent illumination. Flg-injections into the striatum retrogradely labeled neurons in the midbrain. There was a 35% decrease ($p<0.009$) in the number of Flg labeled SNc cells in the ischemic hemisphere (85.5+18.2) as compared to the non-ischemic hemisphere (132.4+22.7). The reduced number of projection neurons in the ischemic henmisphere is consistent with the loss of trophic support from the striatum. SNc neurons are a critical component of reward pathway and motor function, hence degeneration of these neurons could lead to long term motor deficits and depressive symptoms including anhedonia that are common after stroke. This study has been supported by NIH AG042189.

6. **The short term effects of acute clomipramine treatment and maternal care on microRNA-16 expression in the dorsal raphe of neonatal rats**. Department of Psychology and Neuroscience, Colgate University, Hamilton, NY Connor Dufort; Christina M. Ragan. A mammal's early life environment including its maternal treatment has lasting consequences for the development of anxiety-like behavior and serotonin regulation. Increasingly, children are exposed to antidepressants via their mother in utero and as infants through breastfeeding. The long term effects of early antidepressant exposure with respect to anxiety are relatively unknown in humans, but the lasting anxiolytic effect of increased early-life maternal care is well studied in rats. However, compared within a litter of rats, animals that receive more maternal care, measured in licking, during the early postnatal period tend to have higher adult levels of anxiety-like behaviors than their lower-licked siblings. Serotonin reuptake inhibitors (SRIs), commonly used to treat anxiety, alter a developing animal's serotonergic circuits in the dorsal raphe nucleus (DR). microRNA-16 (miR-16) is a noncoding negative regulator of serotonin transporter expression that may contribute to the antidepressant and anxiolytic effects of SRIs. When neonatal rats receive acute 7-day exposure to clomipramine, an SRI, from postnatal day (PND) 4-10, expression of miR-16 was increased in the DR at PND 90 compared to saline-treated animals. Clomipramine treatment is associated with different neurochemical effects in male and female animals depending on the amount of maternal licking bouts received: low-licked female animals express less miR-16 in the DR and low-licked males express more. In the present study, we examined the short-term effects of neonatal clomipramine treatment and maternal behavior by administering either 15 mg/kg of clomipramine or saline to rat pups twice daily from PND 4-10. Maternal licking was observed and recorded four times daily on PND 4, 6, 8, and 10 to determine differences in treatment between siblings. Pups were sacrificed on PND 11 immediately after the end of drug treatment. After quantitative PCR analysis, we found that clomipramine treatment decreased miR-16 expression in the DR. Again, low-licked clomipramine treated female pups tended to express further decreased miR-16 expression in the DR compared to high-licked females and low-licked males. The discrepancy between the long and short-term effects of neonatal clomipramine treatment and maternal behavior introduces the possibility of behavioral and pharmacological interventions that influence the development of the dorsal raphe nucleus and subsequent anxiety behavior in adulthood.

7. **Coordination of orofacial motor actions with respiration in the rat during ingestive, exploratory, and foraging behaviors**. Song-Mao Liao1, Hiteshwar Rao2, David Kleinfeld1,3,4. 1Department of

Physics, University of California, San Diego, La Jolla, CA 92093, USA, 2Department of Bioengineering, University of California, San Diego, La Jolla, CA 92093, USA, 3Section of Neurobiology, University of California, San Diego, La Jolla, CA 92093, USA, 4Department of Electrical and Computer Engineering, University of California, San Diego, La Jolla, CA 92093, USA. Rodents perform orofacial motor behaviors, which include sniffing, whisking, head bobbing, licking, chewing, nose twitching, and vocalizing, as a means to sample their peripersonal space as well as to ingest nutriments. The motor actions must be exquisitely coordinated, not only to efficiently execute environmental sampling routines but also to maintain the patency of the upper airway. Here we address the nature of this coordination to shed light on the neuronal connectivity among the different premotor central pattern generators that are embedded in the brainstem and orchestrate the rhythmic motor outputs. We record the ingestive and exploratory behaviors of rats with microelectronic sensors and videography, along with the electromyogram (EMG) of the underlying muscles and the concurrent respiration. We found that the exploratory head-bobbing is phase-locked with sniffing. The onset of inspiration drives a sampling cycle of the peripersonal space; this involves movement of the head, along with the vibrissae and nose, that is phase-locked to breathing. In ongoing work, we found that the tongue and jaw movements are phase-locked to each other and to breathing during licking. The licking rate is paced near 7 Hz, while the ratio of the licking cycles to the breathing cycles forms a discrete and breathing-dependent temporal pattern. The chewing rhythm is paced near 6 Hz and the tongue will preferentially phase-lock to chewing over breathing. No temporal relationship between chewing and breathing is observed, consistent with two independent brainstem oscillators in orofacial control. We are extending this approach to study the coordination of orofacial motor actions with respiration cycles during exploratory and foraging behaviors performed by the rat in an open field. Supported by US NIH grants NS0905905 and NS058668, US NSF EAGER grant 2144GA, and the Taiwan Studying Abroad Scholarship to S.-M. L.

8. **Lowering luteinizing hormone (LH) prior to hippocampal damage (in an Alzheimer's disease model) can mitigate the loss of spatial memory in female rats.** Thornton, Janice; Chang-Weinberg, Janie; Curley, Emily; Natowicz, Rebecca. Department of Neuroscience, Oberlin College, Oberlin, OH. Luteinizing hormone increases after menopause or ovariectomy (ovx) in females and high levels of LH have been associated with Alzheimer's disease (AD) in humans. In female rats and mice, LH increases amyloid-beta levels and decreases spatial memory. These effects are independent of estrogen levels. Previously, we have shown that ovx rats in a hippocampal damage model of early AD showed decreased spatial memory that was mitigated when LH was decreased beginning before and extending after hippocampal damage. The present study explored whether decreasing LH only prior to hippocampal damage would help prevent memory loss. To create a model of early AD, 1 µl of the neurotoxins amyloid-beta (4 µg/µl: pre-aggregated for 4d) and ibotenic acid (1µg/µl) were stereotaxically infused bilaterally into the hippocampus of adult female Sprague-Dawley rats. To vary LH levels, rats were either ovx and given vehicle so they had high LH levels or were ovx and given Antide (1mg/kg, sc), a GnRH antagonist that decreases LH levels. This resulted in three groups: No AD (infusion of vehicle and injection of vehicle); AD (infusion of neurotoxins and injection of vehicle) and AD+Antide (infusion of neurotoxins and injection of Antide). The Antide or vehicle were administered 1d prior to the neurotoxin infusion. One week after recovery females were habituated and tested for spatial memory using the Object Location Test with an inter-trial interval of 10min. Animals were tested 3x with 4 -6d between tests and data were averaged. The ovx No AD females showed clear

preference for the moved object, indicating good spatial memory. The AD females (Ovx females infused with the neurotoxins) did not discriminate between moved and unmoved objects. Antide, when injected 1d prior to neurotoxin infusion (AD+ Antide group) counteracted the effects of the neurotoxin infusion on spatial memory: Females again showed a clear preference for the moved object. These results suggest that high levels of LH such as those seen after menopause may contribute to the damage seen during AD, and that an LH antagonist could play a preventative role in treatment of the cognitive impairment seen in Alzheimer's disease.

9. **Maternal Brain and Parenting Stress**. Madoka Noriuchi 1,2. Kumiko Mori 1. Yoko Kamio 2. Yoshiaki Kikuchi 1. 1 Div. of Human Health Sciences, Graduate School of Tokyo Metropolitan University. 2 Dept. of Child and Adolescent Mental Health, National Institute of Mental Health, National Center of Neurology and Psychiatry. Feeding, which protect child life and promote child growth, is an essential behavior that provides an opportunity for interaction between mother and her child and therefore, is important for the mother-child bonding. On the other hand, to look after the "terrible twos" often causes parenting stress. Here, we investigated the brain response of the mothers for infant feeding situation by using fMRI. Then, the correlation between the brain activity and the parenting stress was examined. [Methods] 28 healthy right-handed mothers of 2-3-year-old child gave informed consent to participate in this study. We edited 4 different clips (30s) from each recorded child feeding situation. At the fMRI, the 4 clips of the own child and 4 other unknown children were presented randomly. The fMRI using a T2-weighted EPI and T1-weighted images were acquired by using a 3T MRI device (Achieva Quasar Dual, Philips). To investigate the relationship between the brain activity and daily parenting stress, mother rated the Japanese version of the parental stress index (PSI) based on the original version (Abidin, 1983). The fMRI data were analyzed separately using SPM8. Each situation was modeled using a separate repressor for each participant after preprocessing. The contrasts between the brain activity for the own child and other children were examined. Random effects analysis was then performed. Moreover, correlation analyses were carried out for associations between the brain activity and the PSI ($p < .05$). [Results] We found the brain regions related to maternal love, motivation of maternal behavior (OFC, PAG, Insula) and appropriate response including mind-reading (pSTS, FG, TP, IFG, CB) for mother's own child compared with other children. Among them, the activity in the OFC was negatively correlated with parent domain among the PSI. On the other hand, CB was negatively correlated with the child domain among the PSI. These findings may provide useful scientific evidence for supporting mother-child psychotherapy.

10. **Determining the mechanistic relationship between Toxoplasma infection and deficits in amphetamine induced activity**. McFarland, Ross1; Weng, Zi Teng2; Yolken, Robert H1,3; Pletnikov, Mikhail1. Infection with the neurotropic parasite Toxoplasma gondii has been an identified environmental risk factor for the development of schizophrenia in human populations. In animal models of the disease, long term latent infection with the parasite has been associated with a wide range of behavioral changes. These changes have typically been characterized by relatively weak effects that are highly dependent on the genetic background of both the rodent host as well as the parasite. Most critically, a definitive mechanistic explanation of how the parasite is impacting behavior has been largely elusive. In this work, we present results indicating that infection with Toxoplasma causes significant impacts on dopamine(DA) release in infected mice, specifically disrupting neurochemical signaling during stimulant drug administration. The impact on animal behavior

includes significant deficits in host response to the stimulant drugs amphetamine and cocaine. This disruption is independent of any significant damage to synaptic density in the striatum resulting from infection. Furthermore, it is also independent of several key host factors regulating DA release, as well as production of tyrosine hydroxylase from the parasite itself. These findings suggest chronic infection with Toxoplasma is inducing an inflammatory response that significantly interferes with the function of DA release and signaling in the host brain.

11. **Exosomal MHCI derived from astrocytes leads to behavioral and neuropathological abnormalities in mice**. Akira Sobue1, Norimichi Ito1, Kazuhiro Hada1, Akira Nakajima1, Toshitaka Nabeshima2, Taku Nagai1, Kiyofumi Yamada1. 1Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine. 2Advanced Diagnostic System Research Laboratory Fujita Health University, Graduate School of Health Sciences & Aino University. The major histocompatibility complex (MHC) is well-known as a series of genes that code for cell surface proteins which play an important role in the adaptive immune response. Genome-wide association studies have implicated the MHC gene region on chromosome 6p21.3-22.1 in schizophrenia. The MHC genomic region in the mouse, located on chromosome 17, is named H-2 and the genes within this region are classified into three distinct classes (I to III). The MHC class I (MHCI) genes, such as H-2K and H-2D in the mouse, are highly polymorphic, and the unique roles of MHCI molecules have been demonstrated in the central nervous system. However, the pathopsychological role of MHCI in schizophrenia remains unclear. We have previously reported that polyriboinosinic-polyribocytidylic acid (polyI:C) treatment in neonatal mice results in impairments of neurodevelopment, which is accompanied by schizophrenia-like behaviors in adulthood. Neonatal polyI:C treatment increased MHCI H-2K and H-2D mRNA levels in the medial prefrontal cortex (mPFC). PolyI:C treatment in cultured astrocytes but not in neurons also increased the MHCI mRNA levels. Moreover, we have previously demonstrated that MHCI/H-2D or its soluble form sMHCI/sH-2D is secreted into the exosomes from astrocytes. To clarify the role of MHCI in astrocytes, we developed a mouse model expressing MHCI molecules in astrocytes of mPFC, using an adeno-associated virus (AAV) vector that expresses the transgene under the control of glial fibrillary acidic protein (GFAP) promoter. Behavioral and neuropathological analyses were carried out 3 weeks after the AAV injection. The astroglial expression of MHCI in the mPFC impaired social behavior and object recognition memory in mice. Moreover, the number of Iba1-positive microglial cells was significantly increased in the mPFC of MHCI-expressed mice compared with control mice. Astroglial expression of MHCI decreased the number of parvalbumin-positive cells and reduced the dendritic spine density of pyramidal neurons in the mPFC. Moreover, repeated treatment of neutral-sphingomyelinase inhibitor GW4869 ameliorated these impairments of sociability and recognition memory and changes in Iba1-possitive microglia. These results suggest that the exosomal MHCI derived from astrocytes affects the microglial proliferation as well as neuronal number and spine density, thereby leading to behavioral dysfunctions in mice.

12. **Olfactory bulbectomy in methamphetamine rat mothers induces impairment in morphological and functional development of their offspring**. Slamberova Romana1, Ruda-Kucerova Jana2, Babinska Zuzana2, Sevcikova Maria 1. 1 Charles University, Third Faculty of Medicine, Department of Normal, Pathological and Clinical Physiology, Prague, Czech Republic. 2 Masaryk University, Faculty of Medicine, Department of Pharmacology, Brno, Czech Republic. Olfactory bulbectomy in rodents is

considered a putative model of depression. Depression is often associated with drug addiction. Our previous studies demonstrated that methamphetamine (MA) administration to rat mothers affects both, behavior of the mothers and their pups. The aim of the present study was to examine the effect of bulbectomy and MA administration on behavior of rat mothers and postnatal development of their pups. At the beginning of the behavioral and neurochemical experiments, adult female Wistar rats were randomly divided into two groups: bulbectomized (OBX) and sham-operated (SH). A period of 20 days was allowed for the development of the depressive-like phenotype. Animals were tested in the motor activity test and 2% sucrose preference for anhedonia and hyperactive locomotor response to a novel environment, respectively. After then females were impregnated. Pregnant females were exposed to daily subcutaneous (s.c.) injection of MA (5 mg/kg) or saline (SA) during the entire gestation period. Postnatally, maternal behavior and pup development was examined. The effect of challenge dose of MA (1 mg/kg, s.c.) on behavior was further examined in adult male offspring. Our results showed no differences in the maternal behavior as a matter of bulbectomy, only OBX rats slept more than all the SH controls. Pups from OBX mothers were born with lower birthweight and gained less weight during the postnatal development than pups from SH controls. Both, bulbectomy and MA administration, delayed the eyes opening. As a matter of functional development of the pups, maternal OBX procedure impaired the performance in the Bar-holding test, but only in saline group. OBX/SA group was the worst in the Bar-holding test relative to all the other groups. In addition, pups from OBX mothers dropped more boluses during the Bar-holding test, suggesting that they were more stressed. In adult male offspring, bulbectomy increased immobility only in the SA/SA group. Prenatal MA exposure increased locomotion, while decreasing immobility. In addition, challenge dose of MA in adulthood increased distance traveled, locomotion, rearing, and average and maximal velocity, while decreasing immobility and grooming. In conclusion, our results suggest that depressive-like phenotype of rat mothers induces impairment in morphological and functional development of their male offspring. Supported by: Progres Q35, MUNI/A/1063/2016.

13. **Fos expression in the hypothalamus and brainstem after tail suspension in rats.** Takashi Maruyama, Yasuhito Motojima, Mitsuhiro Yoshimura, Hirofumi Hashimoto, Satomi Sonoda, Hiromichi Ueno, Reiko Saito, Yoichi Ueta. Department of Physiology, School of Medicine, University of Occupational and Environmental Health, 807-8555 Japan. Tail suspension that induces hindlimb unloading is one of the microgravity environment models which can observe the effect by living in space for mammal body. Microgravity is known as one of the causes of musculoskeletal atrophy and stress. However, the biological mechanism of microgravity for central nervous system is unexplained. The neurohypophysial hormones, oxytocin (OXT) and arginine vasopressin (AVP), are mainly synthesized in the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus. Originally OXT is known for its important role in stimulating uterine contractions and milk ejection, while AVP plays a role for water homeostasis by regulating urine concentration. These peptides, OXT and AVP are now understood to mediate social behaviors in mammals. In addition, some studies indicate that OXT is related with the mental stress and musculoskeletal construction. In the present study, we investigated Fos expression in the SON, the PVN, brainstem, the vestibular nucleus (VN) and the nucleus tractus solitaries (NTS) 1.5 and 24 hours after tail suspension in adult male Wistar rats, using immunohistochemistry. The numbers of Fos-immunoreactive (ir) neurons in the SON, the PVN and the NTS were significantly increased 1.5 hours but not 24 hours after tail suspension. Double immunostaining for Fos and either OXT or AVP revealed that OXT-ir neurons rather than AVP-ir

neurons in the SON and PVN mainly exhibited Fos-ir in tail suspended rats. These observation's physiological meanings should be qualified by further study. This study was performed with the support of Scientific Research on Innovative Areas ("Living in Space") from the Japan Society for the Promotion of Science.

14. **Involvement of iCA1? mPFC pathway in the processing of episodic-like memory in rats**. Jay-Shake Li, Hsu-Ching Hung. Department of Psychology, National Chung Cheng University, Taiwan. Many researchers define the episodic-like memory as animals' ability to combined what, where, and when elements to form an integrated memory system, and utilize it as a model to study neural mechanism of episodic memory in human. Previous studies have shown that, both hippocampus and medial prefrontal cortex (mPFC) are essential for the episodic-like memory processing in rats. Furthermore, anatomical studies indicated that neurons in the hippocampal intermediate CA1 region project heavily on the mPFC. In return, the mPFC sends information back to hippocampus indirectly via some thalamic nuclei. However, functional roles of the neural circuit in the processing of episodic-like memory are not well understood. In particular, the functional connections between the two regions across the hemisphere have not been investigated yet. In the present study, we injected lidocaine to temporarily inhibit neural activity of intermediate CA1 and mPFC at ipsi- or contralateral sites, and observed episodic-like memory of rats for a fear conditioning event. The memory processing in the behavioral task could be divided into three stages: 1) formation of spatial-temporal pair-association, 2) encoding of an electrical foot-shock event, and 3) episodic retrieval of the event. The lidocaine inhibitions were applied before the tree stages, and could specifically influence the pair-association, the encoding, and the retrieval process of episodic-like memory. The results showed that, the ipsilateral manipulations given before all three stages revealed no effect on the performances of rats, while contralateral inhibitions before the foot-shock conditioning and before the final test impaired animals' performances. In conclusions, the processing of episodic-like memory requires the cooperation of intact mPFC and hippocampal intermediate CA1 on at least one hemisphere of the brain.

15. **Prenatal stress on Gad1-heterozygotes selectively perturbs parvalbumin (PV)-positive GABAergic neurogenesis, GABA synapses and social interaction behavior.** Tianying Wang1, Adya Saran Sinha1, Yuchio Yanagawa2, Tomoko Kawai3, Kenichiro Hata3, and Atsuo Fukuda1. 1. Dept. Neurophysiol., Hamamatsu Univ. Sch. Med., Hamamatsu, Japan. 2. Dept. Genet Behav Neurosci, Gunma Univ. Grad. Sch. Med., Maebashi, Japan. 3. Dept. of Maternal-Fetal Biology, Natnl. Res. Inst. Child Health Dev., Setagaya, Tokyo, Japan. Exposure to prenatal stress (PS) and mutations in Gad1, which encodes the GABA synthesizing enzyme glutamate decarboxylase (GAD) 67, are both risk factors for psychiatric disorders. In addition, disturbance of PV-positive GABAergic interneurons in the medial prefrontal cortex (mPFC) and hippocampus (HIP) has often been observed in schizophrenia and autistic patients. To elucidate their relationship, we examined GAD67-GFP knock-in mice (GAD67+/GFP) that underwent PS from embryonic day 15.0 to 17.5. Administration of BrdU revealed that neurogenesis of GABAergic neurons was significantly diminished in fetal brains during PS. Postnatally, the density of PV-positive, but not PV-negative, GABAergic neurons was significantly decreased in the mPFC, HIP and somatosensory cortex of GAD67+/GFP mice. By contrast, these findings were not observed in wild type offspring, suggesting that prenatal stress in addition to Gad1 anomaly could specifically disturb the proliferation of neurons destined to be PV-positive. We also found fukutin (Fktn) responsible for Fukuyama type congenital muscular dystrophy was hypermethylated. Fktn glycosylates α-

dystroglycan (α-DG) which is associated with GABAergic synapses and promotes plasticity. We found glycosylation of α-DG and frequency of miniature IPSCs were significantly decreased in the mPFC. Behavioral phenotype showed anomalous social interaction. These findings may provide new insights into underlying mechanisms of the pathogenesis of psychiatric disorders.

16. **EEG and heart rate synchronization with oscillating OLED light**. Emi Yuda1, Hiroki Ogasawara1, Yutaka Yoshida1, and Junichiro Hayano1. 1Nagoya City University Graduate School of Medical Sciences. Enhancement of 0.1 Hz fluctuation in respiration and heart rate has been used as a method for inducing relaxation. To investigate if heart rate can be entrained with oscillating light at 0.1 Hz, we examined the effects of oscillating light exposures on heart rate variability (HRV) and electroencephalogram (EEG) using organic light-emitting diodes (OLED) that is known as non-glaring and comfortable lighting source. Using an experimental ceiling light system consisting of 120 panels (55 x 55 mm square) of OLED modules with adjustable color and brightness, 10 healthy young subjects underwent 10-min exposure to oscillating (0 to 100% with sinusoidal function) and constant (100%) OLED lights alternately for 4 times each in supine position just under the light. We examined red (54 lx at 100%) and green (69 lx) OLED lights at the same clock time on separates days at 1-week interval. Time dependent changes in the amplitudes of HRV were analyzed for high frequency (HF; 0.15-0.45 Hz) and low frequency (LF; 0.04-0.15 Hz) components and those of EEG for α (8-15 Hz), β (16-31 Hz), θ (4-7 Hz), and δ (<4 Hz) waves by complex demodulation. The coherences and phase relationships between these amplitudes with oscillating light were analyzed by cross spectrum. No significant coherence or phase relationship with the red or green oscillating light was detected in either HF or LF amplitudes. Whereas, 0.1-Hz oscillating light increased 0.1-Hz oscillation of EEG α wave amplitude ($P = 0.008$) and the effect was greater in red light than green light ($P = 0.06$). Although neither oscillation nor color of light affected the power of α wave or β wave, the oscillation of light lowered the power of δ wave irrespective of color. Cross spectral analysis revealed opposite phase relationship between α wave and illuminance of oscillatory light. Oscillating OLED illumination at 0.1 Hz causes opposite-phase oscillation in α-wave amplitude of EEG, while it does not affect LF and HF amplitudes of HRV.

17. **Rapid estrogenic mediation of oxytocin in social recognition in female mice.** Pietro Paletta1, Kirstyn Ali2, & Elena Choleris1. 1Department of Psychology and Neuroscience Program, University of Guelph, ON, Canada, 2Department of Biological Science, University of Guelph, ON, Canada. An essential aspect of being a social species, like humans and mice, is being able to identify others that may be familiar based on information received from previous encounters. This ability is referred to as social recognition (SR) and is important for the development of social bonds, dominance hierarchies, and various other aspects of social life. Both estrogens and oxytocin (OT) have been previously shown to influence SR in mice. It has been shown that when estrogen receptor alpha (ER□), OT, and the oxytocin receptor (OTR) are each knocked out SR is impaired to some extent. This suggests that both estrogens and OT are needed for proper SR functioning. A model was developed to provide an explanation of these effects that suggests estrogens mediate the production and release of OT and OTR. It suggests that estrogens bind to estrogen receptor beta (ER□) located on the OT producing cells in the paraventricular nucleus (PVN) that facilitates the production and release of OT. OT is transported through projections from the PVN to the medial amygdala where estrogens bind to ER□ to facilitate the production of OTR. OT binding to its receptor in the medial amygdala then facilitates SR. The purpose of this research is to determine whether this is an accurate depiction of how

estrogens and OT interact to facilitate SR. The first step in doing this is to determine whether 17□-estradiol infused into the PVN can facilitate SR in female, CD-1 mice. My current results have shown 17□-estradiol, at the doses of 25nM and 50nM, infused into the PVN can rapidly facilitate SR. This suggests that estrogens in the PVN do rapidly influence SR. The next step is to determine if the rapid effect of 17□-estradiol in the PVN on SR occurs through an interaction with OT. To test this ovariectomized mice will have two bilateral cannulae implanted, one into the PVN and one into the medial amygdala. They will then be given an infusion an OTR antagonist into the medial amygdala and an infusion of 17□-estradiol into the PVN and will be run through a "difficult" SR paradigm. The paradigm will begin 15 minutes after the infusion of 17□-estradiol, where they will be presented with two stimulus mice (habituation) and, after a delay, will be presented with two mice again, one from the habituation phase and a novel stimulus mouse. It is designed to be difficult so that the control mice do not show recognition, so that any enhancing effects that the treatment might have can be observed and the paradigm takes place within 40 minutes to test the rapid effects estrogens have on SR. Since mice have a natural inclination to investigate novelty, if it investigates the novel mouse more than the other mouse, it would suggest that that mouse is familiar to them and there is SR. It is expected that the OTR antagonist in the medial amygdala will block the facilitating effect of 17□-estradiol on SR. This would suggest that estrogens interact with OT to rapidly facilitate social recognition. Funded by NSERC.

18. **Abnormalities in perineuronal nets (PNN) and behavior in CSGalNAcT1 knockout mice which lacks a key enzyme in chondroitin sulfate synthesis**. Michihiro Igarashi1, 2, Nozomu Yoshioka1, 2, Kosei Takeuchi1, 3, Atsushi Tamada1, 2, Hiroshi Kitagawa4, Keizo Takao5, Tsuyoshi Miyakawa6. 1Department of Neurochemistry and Molecular Cell Biology, Graduate School of Medical and Dental Sciences, and 2Transdiciplinary Research Program, Niigata University, Asahi-machi, Niigata, Japan; 3Department of Biology, School of Medicine, Aichi Medical University, Nagakute, Japan; 4Department of Biochemistry, Kobe Pharmaceutical University, Kobe, Japan; 5Division of Experimental Animal Resource and Development, Life Science Research Center, Toyama University, Toyama, Japan; and 6Division of Systems Medical Science, Institute for Comprehensive Medical Science, Fujita Health University, Toyoake, Japan. Chondroitin sulfate (CS) is an important glycosaminoglycan and is found in the extracellular matrix as CS proteoglycans. In the brain, CS proteoglycans are highly concentrated in perineuronal nets (PNNs), which surround the synapses and modulate their functions, and PNN abnormalities in relation to human mental diseases have been reported. To investigate the importance of CS, we produced and precisely examined mice that were deficient in the CS synthesizing enzyme, CSGalNAcT1 (T1KO). Biochemical analysis of T1KO revealed that loss of this enzyme reduced the amount of CS by approximately 50% in various brain regions. The amount of CS in PNNs was also much more diminished in T1KO than wild-type mice, although the amount of a major CS proteoglycan core protein, aggrecan, was not changed. In T1KO, we observed abnormalities in several behavioral tests representing higher brain functions. These results suggest that T1 is important for plasticity, probably due to regulation of CS-dependent PNNs, and that T1KO is a good animal model for investigation of PNNs.

19. **An open-source 3D video based behavioral analysis systems for rodents and monkeys.** Jumpei Matsumoto1, Hiroshi Nishimaru1, Yusaku Takamura1, Taketoshi Ono1, Hisao Nishijo1. 1University of Toyama. Three-dimensional video based behavioral analysis allows various experiments and analyses

more efficiently, which have been difficult with 2D video based systems. However, such potential benefits have largely been unexplored, due to a relatively high cost and technical difficulties to set up and utilize 3D video based systems. To facilitate applications of 3D video analysis, we are going to launch an open-source project for a low-cost (<3,000 dollars), versatile 3D video analysis system, with rich documentations and an online community that help users (URL). The project is based on a system previously developed by the authors, which utilize multiple depth cameras to reconstruct a 3D video and estimate the positions of body parts by fitting skeletal models to the 3D video. The features of the present system are: 1) capacity to analyze multiple animal species (rodents and monkeys); 2) robust tracking during overlap (e.g., social interaction); 3) estimating detailed 3D posture without any markers on the animals; 4) fast pose estimation algorithm capable of real-time detection of specific behavior. These features allow various experimental designs by combining with other techniques such as electrophysiology and optogenetics. We call for collaborators (both of users and developers) to improve the software and the documentations. In the poster, we will show the outline of the project and the present system, and discuss possible applications and future improvements.

20. **Nesfatin-1/NucB2 Neurons in the Hypothalamus and Brainstem Activated by Intraperitoneally Administered Cisplatin in Rats.** Yoichi Ueta1, Mitsuhiro Yoshimura1, Satomi Sonoda1, Hiromichi Ueno1, Yasuhito Motojima1, Reiko Saito1, Takashi Maruyama1, Hiroshi Hashimoto1, Yasuhito Uezono2. 1Department of Physiology, School of Medicine, University of Occupational and Environmental Health, Japan. 2Division of Cancer Pathophysiology, National Cancer Center Research Institute, Tokyo, Japan. Cisplatin has been widely used as an anti-cancer drug that inhibits the replication of DNA. However, various disadvantageous side effects, including anorexia, afflict patients. Nesfatin-1, recently identified satiety molecule derived from NucB2, is broadly expressed in the central nervous system (CNS) and peripheral organs. In the present study, we aimed to clarify the relation between activation of nesfatin-1/NucB2 neurons in the CNS and anorexia after intraperitoneal (i.p.) administration of cisplatin. Saline, as control, or cisplatin (6 mg/kg) was administered in adult male Wistar rats (180-200 g). Food intake and body weight were significantly decreased over 3 days after i.p. administration of cisplatin. Ninety min after i.p. administration, they were perfused, followed by carrying out double-immunohistochemistry for Fos and nesfatin-1/NucB2. The examined nuclei were as follows: organum vasoculum lamina terminalis (OVLT), median preoptic nucleus (MnPO), subfornical organ (SFO), supraoptic nucleus (SON), paraventricular nucleus (PVN), arcuate nucleus (ARC), lateral hypothalamic area (LHA), ventral tegmental area (VTA), dorsal raphe nucleus (DR), locus coeruleus (LC), area postrema (AP), nucleus tractus solitarius (NTS), rostral ventrolateral medulla (RVLM). Many nesfatin-1/NucB2 neurons expressing Fos-like immunoreactivity were observed in the SON, PVN, ARC, LHA, VTA, DR, LC, AP, NTS, RVLM 90 min after i.p. administration of cisplatin. Intracerebroventricular administration of nesfatin-1/NucB2 antisense resulted in significant attenuation of decreased food intake after i.p. administration of cisplatin for 180 min compared to the group which received the missense. These results suggest that i.p. administration of cisplatin activated, at least in part, nesfatin-1/NucB2 neurons in the various regions of the CNS and may exert anorexic effects.

21. **Effects of vestibular lesion on hypothalamic feeding-regulating neuropeptides after being exposed to hyper gravity in mice**. Satomi Sonoda1, Mitsuhiro Yoshimura1, Hiromichi Ueno1, Yasuhito Motojima1, Reiko Saito1, Takashi Maruyama1, Hirofumi Hashimoto1, Hironobu Morita2, and Yoichi

Ueta1. 1Department of Physiology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan. 2Department of Physiology, Graduate School of Medicine, Gifu University, Gifu, Japan. Space sickness is thought to be caused by inappropriate integration of the information from the vestibular systems in the different gravity environment. In the present study, we examined the effects of the exposure of different gravity with/without the vestibular lesion on the gene expressions of the hypothalamic feeding-regulating neuropeptides in mice. To delete the vestibular function, we conducted vestibular lesion by a laser. Adult male C57BL/6J mice were received sham operation (Sham) or vestibular lesion (VL) before the experiment. After the recovery, they were divided into 4 groups: Sham-1g, VL-1g, Sham-2g, and VL-2g (n=6 in each) and exposed to 1g or 2g environment with centrifugation of custom-made gondola-type rotating box for 3 days, 2 weeks, and 8 weeks. At the end of the each time point, they were decapitated. The brains were removed immediately and frozen on dry ice and then stored at -80 C. They were cut into 12 µm thickness by cryostat. The locations of the hypothalamic areas, including the paraventricular nucleus (PVN), arcuate nucleus (ARC), and lateral hypothalamic area (LHA), were determined according to coordinates of the mouse brain atlas. The gene expression of the corticotrophin releasing hormone (CRH) in the PVN, propiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript (CART), neuropeptide Y (NPY), agouti-related peptide (AgRP) in the ARC, melanin-concentrating hormone (MCH), and orexin in the LHA were quantified by using in situ hybridization histochemistry. VL did not affect all neuropeptides which we investigated at each time point. After 3 days exposure, NPY, AgRP and orexin were significantly increased, whereas, POMC and CART were decreased in Sham-2g and VL-2g compared to Sham-1g. CRH was significantly increased in Sham-2g compared to Sham-1g, however, that in VL-2g were not. After 2 weeks exposure, CRH and POMC was significantly increased in Sham-2g compared to Sham-1g, while those were not in VL-2g. After 8 weeks exposure, all neuropeptides which we examined were comparable among the groups. These results suggest that the gene expression of the hypothalamic feeding-regulating neuropeptides are affected by different gravity, and the gene expression of the CRH and POMC are, at least in part, thought to be received neuronal input from the vestibular systems.

22. **Dorsal raphe serotonin-containing neurons in rats are postsynaptically depolarized by both orexin and ghrelin through PLC-PKC signaling pathway: An in vitro study**. Juhyon Kim, Masaki Ogaya, Kazuki Nakajima and Kazuo Sasaki. Div. of Bio-Information Engineering, Fac. of Engineering, University of Toyama, Toyama 930-8555, Japan. Serotonergic (5-HT) neurons in the dorsal raphe nucleus (DRN) play a crucial role in a wide variety of physiological functions including feeding, sleep/wake, anxiety, depression and cognition. In a previous electrophysiological study, it has been reported that putative DRN 5-HT neurons identified on the basis of their electrophysiological and/or pharmacological properties are all excited by orexin. Our electrophysiological study also showed that ghrelin depolarizes two-third of putative 5-HT neurons in the DRN. As well known, orexin and ghrelin are brain-gut peptides and they bind to G protein-coupled receptors which induce an activation of Gq protein. Thus, we hypothesized that both orexin and ghrelin may excite same putative DRN 5-HT neurons through a common signaling pathway. To test this hypothesis, we examined electrophysiological effects of orexin and ghrelin on putative 5-HT neurons in the DRN using rat brain slice preparations. Whole-cell patch clamp recording revealed that about 60% of putative 5-HT neurons are postsynaptically depolarized by both orexin and ghrelin. Simultaneous application of orexin and ghrelin produced an additive effect on the magnitude of depolarization. On the other hand,

the depolarization induced by orexin and ghrelin was significantly suppressed in the presence of D609, an inhibitor for a phosphatidylcholine-specific phpspholipase C (PLC). Bisindolylmaleimide II, an inhibitor of ATP-competitive protein kinase C (PKC), also suppressed the orexin- and ghrelin-induced depolarization. Finally, we showed immunohistochemically that most of putative 5-HT neurons are actually 5-HT-containing neurons and found that a large number of 5-HT-containing neurons are indeed depolarized by both orexin and ghrelin. Present results suggest that the orexin- and ghrelin-induced depolarization is mediated via a common PLC-PKC signaling pathway and that orexin and ghrelin may play, in part, mutually complementary roles on the DRN 5-HT-containing neurons to mediate the hypothalamic and/or peripheral influences on brainstem machinery which regulates physiological functions.

23. **Behavioral correlates to drug-induced rewiring of striatal circuits**. Louise Adermark, Valentina Licheri, Julia Morud, Amir Lotfi, Mia Ericson, Bo Söderpalm. Addiction Biology Unit, Sahlgrenska Academy, Institute of Neuroscience and Physiology, University of Gothenburg, Sweden. Drug addiction has been conceptualized as maladaptive recruitment of integrative circuits coursing through the striatum, facilitating drug-seeking and drug-taking behavior. By combining a battery of behavioral tests paired with slice electrophysiology and cell biological techniques we show that nicotine produces an assembly of neuronal transformations in the dorsomedial striatum (DMS), a striatal sub-region associated with goal-directed performance. Following protracted nicotine use, however, these neuroadapations are progressively transferred towards striatal areas linked to automatic and habitual responses, where they remain for months after last drug-exposure. These characteristic temporal and spatial neuroadapations coincide with behavioral sensitization, changes in rearing activity and finally anxiolytic behavior. We hypothesize that these progressive transformations, in which neuroadapations are shifted between different striatal circuits, reflects a complete rewiring of striatal circuits. We also postulate that this reorganization play a key role when drug addiction progresses from occasional recreational use towards compulsive, habitual drug intake. This work was supported by the Stiftelsen Psykiatriska Forskningsfonden, Swedish Brain Foundation, and the Swedish Medical Research Council.

24. **Effects of 5-HT1B antagonists on behavior in dopamine transporter knockout mice**. F. Scott Hall, Yasir Saber, Raghad Elhag, and Federico Resendiz-Gutierrez. Department of Pharmacology and Experimental Therapeutics, College of Pharmacy and Pharmaceutical Sciences, University of Toledo, OH, USA. Background. Genetic deletion of the dopamine transporter in mice (DAT KO) induces a syndrome of behavioral effects that are characteristic of ADHD, that include locomotor hyperactivity, and impairments in prepulse inhibition of acoustic startle (PPI) and the cliff avoidance reaction. Moreover, many of these effects can be ameliorated by treatments that are effective in treating ADHD in humans. The most commonly used medications to treat ADHD are psychomotor stimulants. The use of these drugs present several problems that would be alleviated by a non-stimulant alternative. Atomoxetine was produced as an alternative but it also has drawbacks. We have recently shown that DAT KO-induced hyperactivity can be reduced by the 5-HT1B antagonist SB 224289. Here we report further studies with this drug and an exploration of behavioral deficits in male and female mice. Methods. Locomotor activity, PPI and CAR were examined in male and female DAT +/+ and DAT -/- mice. The effects of SB 224289 on the PPI and CAR deficits observed in DAT KO mice were examined, as well as upon DAT KO-induced locomotor hyperactivity. Results. In the current studies, the effects

of DAT KO were found to be sex dependent (the effect of sex has not been previously examined), with greater effects observed in female mice. Effects of SB 224289 were found for all 3 tests, although the effects were most robust in the CAR and locomotor tests. Conclusions. In the present studies the effects of DAT KO on behavior were found to be sex-dependent, with greater effects in females. These findings will require confirmation in subsequent studies. Moreover, we have found additional evidence that antagonism of the 5-HT1B receptor may reverse some deficits in DAT KO mice, encouraging further investigation of this potential novel target for the treatment of ADHD.

25. **Exploring Vocalizations in Adult Interactions: The Risk of Committing a Faux Pas**. Candace Burke1, Sergio M. Pellis1, Theresa M. Kisko2, David R. Euston1. 1Dept of Neuroscience, Univ. of Lethbridge, Lethbridge, AB, Canada. 1 Behavioural Neuroscience, Experimental and Biological Psychology, Philipps-University of Marburg, Gutenbergstr. 18, D-35032 Marburg, Germany. Rodent ultrasonic vocalizations are divided into the 50kHz and 22kHz categories. The 22kHz calls occur in a variety of aversive situations and are fairly uniform, characterized by a single unmodulated frequency (i.e., a flat call). The 50kHz calls, on the other hand, have been associated with appetitive situations and more diverse. In fact, it has been suggested that there are as many as 14 distinct call types. When adult male rats encounter one another in a neutral arena, they may play roughly to establish dominance relationships without escalating to aggression. However, if one partner is devocalized, they invariably escalate to serious biting. Clearly vocalizations mitigate aggression, raising the possibility that there are specific calls ensuring the de-escalation of encounters. A Monte-Carlo shuffling procedure was used to identify vocalization-behavior correlations that were statistically significant in pairs of rats in which both could vocalize or in which one was devocalized. First, we identified a sub-category of call differing from its parental call by frequency, duration and context. We termed this new call the extended flat/trill combination and found it was strongly associated with aggressive situations such as bites and mutual uprights. Second, we discovered that the main difference between the two groups was the situations in which calls with flat components were used. The vocal-vocal pairings used these flat calls in several interactions where the devocal-vocal pairs did not. Third, we found that both animals, regardless of their role in the interaction, needed to make these flat calls. These findings show that at least some ultrasonic calls are used strategically during encounters to facilitate communication. Supported by NSERC (Discovery Grant) and Alberta Innovates Health Solutions.

26. **The Role of the Corpus Callosum on Sustained Attention: A Study of Agenesis of the Corpus Callosum in BTBR T+tf/J Mice**. Fang-Wei Hsu1, Loren Martin1, Erica Iceberg1, Brandon Gonzalez1, Gabriel Allaf1, Jonathan Ladner1, Nicole Erskine1. 1Azusa Pacific University. The corpus callosum is the main commissure of the right and left hemispheres, and consists of over 190 million cross-hemispheric axons that transfer information between the homologous cortical areas of two hemispheres. The anterior part of the corpus callosum is the genu, and it connects the prefrontal cortex between hemispheres. The prefrontal cortex plays a significant role in the function of sustained attention, and the communication between the two hemispheres in the prefrontal cortex is primarily through the corpus callosum. Agenesis of the corpus callosum (AgCC) is a congenital deficiency that affects approximately 1 in 4000 live births. In the current study, the researchers examined the effects of AgCC on sustained attention through a mouse model. The BTBR T+tf/J (BTBR) mice were derived from an inbred strain carrying the nonagouti and wildtype T mutations that were crossed with mice with the tufted allele. The BTBR mice are characterized by the hereditary absence of the corpus callosum and

have severe reductions in the size of the hippocampal commissure. The BTBR mice represented the AgCC population, and C57BL/6J mice served as the control group with a normal functioning corpus callosum. The mice were trained to participate in a sustained attention operant task, in which they had to distinguish a signal impulse from a non-signal impulse by pressing either a left or right lever to receive a food reward. The mice needed to fixate on a stimulus light that briefly flashed for a random amount of time; either 50ms, 75ms, 100ms, 500ms, or no flash. Following the signal or non-signal event, the levers extended into the testing chamber. To receive a food reward, the mice had to press the left lever following a signal event and the right lever following a non-signal event. We hypothesized that AgCC will affect the BTBR mice and cause a deficit in sustained attention ability. We found that the BTBR mice and the C57BL/6J mice have the same level of function on the sustained attention task. Previously we found that spatial working memory performance was similar between these two mouse strains. Together, this research indicates that while the prefrontal cortex is well known for its role in executive functions and is heavily interhemisperically connected via the corpus callosum, it does not seem to depend upon these connections for normal functioning of at least these two executive functions.

27. **Different types of basolateral amygdala neurons show different network-dependent electrophysiological properties**. Yang Y[1], Wang G[2], Shyue S[1]. [1]Department of Biomedical Sciences, and [2]School of Medicine, Chang Gung University, Taiwan. The amygdala is one of the core structures responsible for emotion processing in the brain, and is implicated in several disease states, including anxiety disorder, autism, addiction and temporal lobe epilepsy. The circuitry in basolateral amygdala (BLA) is composed of interconnected pyramidal neurons and several types of interneurons. We characterized the electrophysiological properties of these neurons and their possible interplay in acute mouse slices. The pyramidal neurons can be identified morphologically with a soma diameter of >5 μm and electrophysiologically with relatively low-frequency firing activities upon injection of supra-threshold depolarizing currents. In contrast, the interneurons usually have smaller size (soma diameter <5 μm) and typically fire in a quite higher frequency upon membrane depolarization. The interneurons can further be categorized as stuttered-firing/fast-spiking, delayed-firing/accommodating, and burst-firing neurons according to their firing patterns in response to current injection. To understand the network influence on these neurons, we examined the post-synaptic responses (PSR) to intra-nuclear tetanus stimulation mimicking physiological or pathophysiological neural activities, with or without block of glutamatergic or GABAergic synaptic transmission. Application of GABA-A receptor antagonist bicuculline reduces inhibitory PSR and tends to increase the frequency of action-potential spikes in both pyramidal and inhibitory neurons. In contrast, application of AMPA receptor antagonist CNQX consistently reduces both excitatory and inhibitory PSR as well as spontaneous discharges in all cell types. Simultaneous pair- and triple-recordings were also instituted to verify specific presynaptic inputs and the mutual influences from different neurons. We conclude that in BLA, the activities of pyramidal neurons are constantly dampened and thus regulated by the interneurons, while the discharges of interneurons are dependent upon the presynaptic glutamatergic input from pyramidal neurons.

28. **Mechanisms underlying memory consolidation in sleep**. Constantine Pavlides1,2, Jiyeon Cho1, Krzysztof A. Sypniewski1. 1University of Tsukuba, 2The Rockefeller University. Sharp wave ripples (SPWr), observed in hippocampal EEG during awake consummatory behaviors and slow wave sleep

(SWS) may represent a possible mechanism for sleep-induced memory consolidation. Previously it has been reported that following spatial learning, there is an increase in the number of SPWr, while suppression of SPWr post learning produced long-term memory deficits. In the present study, we investigated the effects of SPWr suppression specifically in sleep on long-term contextual fear memory. Adult, male Long-Evans rats were implanted bilaterally with recording electrodes in the hippocampal CA1, for the detection of SPWr as well as EMG electrodes for determining behavioral state, and stimulating electrodes in the ventral hippocampal commissure (vHC), for the elimination of SPWr. The animals were handled and habituated to recording chamber and parameters for SPWr detection and stimulation thresholds for SPWr suppression were determined, On the day of the experiment, the animals were contextual fear conditioned following which they were placed in a sleep chamber and allowed to sleep. The animals were subdivided into 3 groups: 1) SPWr-suppressed. vHC stimulation immediately upon detection of SPWr; Stimulation control. vHC stimulation 250ms following SPWr detection; and 3) Non-stimulated controls. Fear memory was tested 24h later. Initial data indicate a significant decrease in fear responses to the conditioning context for the SPWr suppressed rats. Naive controls as well as rats which received control stimulation (that did not disturb SPWr), showed normal freezing. Previously we reported that suppression of protein kinase A (PKA) during sleep produced long-term fear memory deficits. In a second set of experiments we will determine whether SPWr may affect sleep-dependent memory consolidation via activation of PKA. These experiments are ongoing. (Supported by KAKENHI #26285161 to CP).

29. **Androgen receptor overexpression leads to a reversible deficit in fear-conditioning in male mice.** Firyal Ramzan1,2, Amber Azam3, Ashlyn Swift-Gallant4, Ashley Monks1,2,3, Iva Zovkic1,3. 1Department of Psychology, University of Toronto at Mississauga, 2Neuroscience, 3Cell and Systems Biology, University of Toronto, 4Department of Neuroscience, Michigan State University. Hormones have a significant effect on fear learning memory. For instance, ovarian steroid hormones, particularly estrogen, facilitate both contextual and cued fear conditioning in female mice. In fact, the estrogen receptor β plays an important role in regulating contextual fear conditioning in both male and female mice. While estrogen and its receptors have been relatively well-studied in the context of fear conditioning, much less is known about the role of androgens (e.g. testosterone) and the androgen receptor (AR) in memory formation. Here, we attempt to fill the gap in the literature pertaining to the modulation of fear conditioning through AR. Previous literature shows mixed results, showing that testosterone either does not affect fear conditioning or leads to an enhanced contextual fear response. We generated transgenic mice that overexpress androgen receptors and compared transgenic males with their wild-type (WT) conspecifics. Behaviorally, we see that global AR overexpression leads to deficits in fear memory, suggesting that effects of AR overexpression are mediated by circulating testosterone. Consistent with this hypothesis, gonadectomy eliminated group differences between AR-overexpressing and WT males, implicating testosterone as a negative regulator of fear memory. Further, when transgenic males are treated with the AR-blocker flutamide, the deficit in freezing is rescued and is comparable to WT controls, substantiating the role of AR as a modulator of fear memory. We additionally found that gene expression for certain genes (including immediate early genes, genes pertaining to synaptic transmission, and growth-related genes) was altered in transgenic males in response to gonadectomy and flutamide treatment. These results suggest a role of AR in modulating fear conditioning memory as well as genetic expression in the CA1 region of the hippocampus. Funding: These studies were supported by a Natural Sciences and

Engineering Research Council of Canada (NSERC) Discovery Grant awarded to Dr. Ashley Monks, as well as an NSERC Grant and Connaught Fund awarded to Dr. Iva Zovkic.

30. **Sildenafil exerts antianxiety-like effect in male mice via oxytocin.** Hein Min Latt[1], Hiroaki Matsushita[1], Yuuri Koga[1], Hiroyuki Michiue[1], Teiichi Nishiki[1] and Hideki Matsui[1]. [1]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan. Oxytocin (OT) is a neuropeptide produced from the hypothalamic paraventricular nucleus (PVN). Systemic OT has an important role in labor and lactation, whereas central OT influences a variety of behaviors including social memory, sexual behavior, maternal care, as well as anxiety-related behavior and stress coping. A previous study showed that axonal release of OT may mediate the inhibition of neurons in the amygdala thereby reducing anxiety. Several studies have demonstrated a significant association between plasma OT levels and major depressive disorders in both humans and animals. These findings have led to the proposal of the OT/OTR system as a promising target for treatment of psychiatric illnesses. Though OT cannot cross the blood-brain-barrier, central release of OT can be produced by peripheral mechanisms as well as administration of exogenous drugs. Sildenafil is a selective inhibitor of phosphodiesterase type 5 enzyme, and is shown to modulate CNS functions including OT signaling. We previously showed that sildenafil increases OT secretion in the PVN, and that it has antidepressant-like effect in male mice, which is dependent on OT signaling. In this study, we examined the antianxiety-like effect of sildenafil in adult male mice via OT signaling pathway. Anxiety-like behaviors in male mice were tested by open field test (OFT) or elevated plus maze test (EPM). Intraperitoneal sildenafil was given to the mice prior to a section of OFT or EPM. Sildenafil significantly increased the time spent in the central area in the OFT compared to the control group. Previously, we showed that sildenafil increased the phosphorylation of cAMP response element-binding protein (CREB) in the hippocampus, which was blocked by the OTR antagonist, and that it had no effect on CREB phosphorylation in OTR-KO mice. In the present study, sildenafil-induced phosphorylation of CREB occurred in amygdala as well, and it was also blocked by the OTR antagonist. OT treatment also increased phosphorylation of CREB in amygdala punched out from brain slices. These results suggested that sildenafil may exert antianxiety-like effect via release of OT and subsequent phosphorylation of CREB in amygdala. (JSPS KAKENHI Grant No. JP15K15031).

31. **Ethanol affects acid sphingomyelinase-induced changes in depression/anxiety state of mice**. L.S. Kalinichenko, M. Reichel, J. Kornhuber, C.P. Müller. Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany. Major depression is a chronic disease with high level of co-morbidity with alcohol dependence (Grant et al., 2007; Lalanne et al., 2015). We suggest the ceramide/acid sphingomyelinase (ASM) system as a crucial mechanism for depression/anxiety-induced alcohol addiction. ASM overexpression or intracranial ceramide injections result in an enhanced anxiety/depression-like behavior and reduced neurogenesis (Gulbins et al., 2013). On the other hand, ethanol induces an increase in ASM activity in cell cultures, which can be blocked by the functional inhibitors of ASM, imipramine and desipramine, widely used as antidepressants (Pascual et al., 2003). Here we investigated interactions between depression and alcohol dependence in animals with dysfunctions of ASM activity. Experiments were performed on ASMtg and ASM knockout mice (ASMko/wt) mice. In the first series of experiments ASMtg mice received ethanol in increasing concentrations (2-16%) on the model of two-bottle free choice drinking. Then anxious/depressive state of animals was estimated in a battery of behavioral tests. In the second series naïve ASMtg and

ASMko/wt mice received ethanol injections (i.p., 2 g/kg) 30 min before each test. We found higher alcohol preference on the model of voluntary drinking in ASMtg mice comparing to wt. Free choice ethanol consumption reversed increased depression level in untreated ASMtg mice, but did not affect behavior of wt. Anxiety level was higher in untreated ASMtg mice comparing to wt mice. In ASMtg mice alcohol had anxiolytic effect in the open field and anxiogenic effect in the elevated plus maze. Ethanol induced a significant reduction in ASM activity in the dorsal hippocampus of ASMtg. Reduced levels of neurotransmitters (serotonin, dopamine, and norepinephrine) typical for depression were reversed by ethanol treatment in several brain structures of ASMtg mice but not wt. In vivo microdialysis study showed that ASMtg animals are characterized by more intense dopamine response, but lower norepinephrine response to ethanol injection both in the dorsal hippocampus and nucleus accumbens. In contrast to voluntary drinking, ethanol injections had depressogenic, but anxiolytic effects on the behavior of ASMtg and wt mice. Ethanol induced an increase in depression level of ASMko/wt mice. Ethanol injections reversed reduced anxiety in ASMko/wt mice. Ethanol treatment did not affect ASM activity in the dorsal hippocampus of study animals. We conclude that voluntary, but not forced treatment with ethanol reverses depression-like behavior in ASMtg mice. We suggest that ceramide/ASM system can serve as a crucial mechanism for development of depression/anxiety-induced alcohol addiction. This work was supported by the IZKF Erlangen (project E13).

32. **Prevention of behavioral abnormalities in the maternal immune activation model**. Rotem Ben Yehuda1 and Ina Weiner1,2. 1School of Psychological Sciences, Tel-Aviv University, Israel. 2Sagol School of Neuroscience, Tel-Aviv University, Israel. Schizophrenia is a neurodevelopmental disorder manifested symptomatically after puberty. The recognition that the formal diagnosis of the disorder is preceded by behavioral and brain abnormalities, has kindled an interest in preventive interventions during this ""prodromal"" period. Clinical studies indicated that atypical antipsychotic drugs (APDs) may reduce risk of progression to first-episode psychosis, but results are controversial. Novel interventions based on pathophysiological mechanisms believed to play a role in schizophrenia such as inflammation and redox dysregulation, are heavily advocated but studies in humans are challenging. Valid animal models of schizophrenia are imperative in this context. Here we used the maternal immune activation (MIA) model which is based on the known association between maternal infection in pregnancy and increased risk of schizophrenia, to test the efficacy of early intervention with two compounds with strong anti-inflammatory and anti-oxidant properties, Omega 3, and N-acetylcysteine (NAC). Offspring of pregnant dams injected on gestational day 15 with the viral mimic poly-I:C or saline, were treated in adolescence (postnatal days [PND] 34-47) with either ω-3 PUFAs (80% EPA, 20% DHA) in food pellets or NAC at 900 mg/l in drinking water, and tested in schizophrenia-relevant tasks in adulthood (PND>90). Prenatal poly-I:C led to deficits in selective attention and executive function as indexed by disrupted performance in latent inhibition (LI) and reversal. Both disruptions were prevented by omega3 whereas NAC was partially effective. These results support the notion that anti-inflammatory/anti-oxidant compounds, which may be more benign that APDs, have a potential to prevent the emergence of behavioral abnormalities following prenatal insults. This work was supported by the Israel Science Foundation (grant no. 467/11) to IW.

33. **Basolateral amygdala and anterior cingulate contributions to effortful choice behavior**. Evan E Hart1, Julian Gerson1, Yael Zoken1, Marisella Garcia1, Alicia Izquierdo1. 1University of California, Los

Angeles. The basolateral amygdala (BLA) and anterior cingulate cortex (ACC) are known to be involved in appetitive behavior, yet their role in cost-benefit choice of qualitatively different rewards (more/less preferred), beyond magnitude differences (larger/smaller), is poorly understood. We assessed the roles of BLA and ACC on effortful choice. Rats were surgically prepared with either cannulae in BLA or NMDA lesions of ACC and trained to stable lever pressing for sucrose pellets on a progressive ratio schedule. Rats were then introduced to a choice: freely-available chow was concurrently available while they could work for the preferred sucrose pellets. Rats in the BLA experiment were infused with either vehicle control (aCSF) or baclofen/muscimol prior to test. BLA inactivations produced a decrease in lever presses for sucrose pellets compared to vehicle, and chow consumption was unaffected. Inactivation had no effect on sucrose pellet preference when both options were freely available. Critically, when lab chow was not concurrently-available, BLA inactivations had no effect on the number of lever presses for sucrose, indicating that primary motivation in the absence of choice remains intact with BLA offline. During a test under specific satiety for sucrose pellets, BLA inactivation rendered animals less sensitive to devaluation relative to control. The effects of BLA inactivations in our task are not mediated by decreased appetite, an inability to perform the task, a change in food preference, or decrements in primary motivation. Similar to BLA inactivation, ACC lesions produced a significant decrease in lever presses for sucrose pellets compared to sham-operated rats (SHAM), and chow consumption was unaffected. Also like BLA inactivations, ACC lesions had no effect on sucrose pellet preference when both options were freely-available. However, in contrast to our BLA findings, when lab chow was not concurrently available ACC lesions reduced the number of lever presses for sucrose pellets. During a test under specific satiety for sucrose pellets, ACC lesions had no effect on response to devaluation relative to SHAM. The effects of ACC lesions are not mediated by decreased appetite, a change in food preference, or changes in value of the preferred reward, and instead may be due to general work aversion. Taken together, BLA supports the specific value and effortful choice of a preferred option, and the ACC supports willingness to exert effort generally. This work was supported by UCLA's Division of Life Sciences Recruitment and Retention Fund (Izquierdo) and NIH T32DA024635-08 (Hart).

34. **An altered neurodevelopmental profile in mice deficient for autism-associated Neurexin1 gene: communicative and motor aspects at an early stage**. Caruso A1,2, Della Notte S 1, Fernandes C3, Scattoni ML4. 1 Center for Behavioral Sciences and Mental Health, Istituto Superiore di Sanità, Rome, Italy. 2 Doctoral School of Behavioral Neuroscience, Sapienza University of Rome, Italy. 3 Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK. 4 Research Coordination and Support Service, Istituto Superiore di Sanità, Rome, Italy. Autism Spectrum Disorders (ASD) are a group of behaviourally defined disorders characterized by abnormal social interactions and communication deficits, patterns of repetitive or stereotyped behaviours, as well as associated symptoms (e.g. motor alterations). Although the causes of ASD remain unclear, evidence strongly supports the role of genetic factors in their aetiology. Both common variations and rare mutations in the genes functioning at synapses in the brain have been identified in autistic patients, including Neurexin (NRXN) family genes. Our research has focused on mice with deletion of Nrxn1α gene encoding for a long isoform of neuronal presynaptic cell-adhesion molecules, with the main aim of investigating the behavioural consequences observed in absence of this gene. Specifically, our study has aimed the behavioural phenotyping of mice in order to identify one or more distinctive autistic-like features, as soon as possible during the early developmental period, since ASD are neurodevelopmental disorders with

early onset of symptoms. We have evaluated the ontogentic profile of the vocal response during the first two weeks of life (postnatal day 2-12) through a detailed analysis of the ultrasonic vocalizations, by comparing Nrxn1α−/− null mutant, Nrxn1α+/− heterozygous and Nrxn1α+/+ wildtype littermate controls. Ultrasonic vocalizations are emitted by mouse pups in response to isolation from the mother and littermates and therefore considered a suitable tool for the identification of early communication deficits in autism mouse models. Moreover, since motor dysfunctions can predict the onset of the other symptoms in ASD, we have performed a fine-grain characterization of spontaneous motor behaviours, recorded simultaneously with the ultrasonic vocalizations. This is the first vocal and motor evaluation of Nrxn1α mutant pups that allows identification of autistic-like phenotypes at an early developmental stage, during which social deficits and other associated behavioural parameters often are difficult to identify. Our results indicate that an altered profile is detectable in the emission of ultrasonic vocalizations and acquisition of specific motor patterns in Nrxn1α mutant pups, in line with behavioural phenotypes observed in ASD children. Our findings suggest that the Nrxn1α gene has an important neurodevelopmental function and its deletion causes specific behavioural abnormalities, thus early deficits can be detected in this genetic model.

35. **Ventral tegmental area-Cav1.3 L-type Ca 2+ channels CaMKII/ERK2/CREB signaling is essential for long-term adaptation in AMPARs in the nucleus accumbens**. A. Martinez-Rivera [1, 2] , Thomas Giordano[1] , Gagan Kaur1 , Joerg Striessnig[3,4] , Nii Addy[5] , Anjali M. Rajadhyaksha[1, 2], [1]Department of Pediatrics, Division of Pediatric Neurology, New York Presbyterian Hospital, [2]Feil Family Brain and Mind Research Institute, Weill Cornell Medical College, NY, NY, [3]Pharmacology and Toxicology, University of Innsbruck, [4]Center for Molecular Biosciences, University of Innsbruck, Innsbruck, Austria, [5]Department of Psychiatry and Department of Cellular and Molecular Physiology, Yale School of Medicine, New Haven, CT, USA; Interdepartmental Neuroscience Program, Yale Graduate School of Arts and Science, New Haven, CT, USA. Human genetic studies have linked the L-type calcium channel (LTCC) genes to multiple neuropsychiatric disorders. In particular, the CACNA1D gene that codes for the $Ca_v1.3$ subunit of LTCCs has been associated with bipolar disorder (BP) and cocaine dependence, highly co-morbid conditions and we recently demonstrated that $Ca_v1.3$ channels within the ventral tegmental area (VTA) to nucleus accumbens (NAc) pathway plays a critical role in cocaine-and depressive-like behavior, highlighting the importance of this gene and channel. However, the molecular mechanisms within the VTA that mediate the cocaine and depressive-like behaviors are still unknown. In the present study, using mutant mice expressing 1,4 dihydropyridines (DHP)-insensitive $Ca_v1.2$ ($Ca_v1.2DHP^{-/-}$) we find that the LTCC blocker nifedipine that specifically targets $Ca_v1.3$ channels in these mice, inhibits cocaine-induced phosphorylation of CaMKIIalpha, ERK, and CREB within the VTA and GluA1 within the NAc. To directly map the $Ca_v1.3$ Ca^{2+} signaling mechanisms that underlie cocaine seeking behavior we utilized cocaine conditioned place preference (CPP). Blockade of CaMKII in the VTA by utilizing KN93 (CaM kinase II inhibitor) before each cocaine conditioning session, attenuated cocaine CPP and cocaineinduced CREB, and ERK phosphorylation, and cocaine-induced GluA1 higher levels within the NAc. Furthermore, blockade of ERK with the ERK inhibitor U0126 or ERK2 siRNA, attenuated cocaine CPP, VTA-CREB phosphorylation and NAc-GluA1, but not VTA-CaMKIIalpha phosphorylation, suggesting that ERK is activated downstream of CaMKIIalpha that then activates CREB. To further explore the neurotransmitter mechanisms that are recruited upstream of VTA $Ca_v1.3$ channels we are currently exploring the laterodorsal tegemental nucleus (LDTg) that sends glutamatergic, GABAergic and cholinergic projections to the VTA and a projection shown to be

sufficient to induce place preference. Our preliminary results using chemogenetic DREADD manipulations demonstrate that inhibition of the LDTg, with hM4Di-DREADD blocked cocaine CPP. However, inhibiting glutamatergic LDTg projections had no effect on cocaine CPP, suggesting a potential role of LDTg cholinergic or GABAergic mechanisms in driving cocaine CPP. Taken together, our findings demonstrate that VTA Cav1.3 channel signaling mechanisms are necessary for cocaine place preference and may recruit the LDTg-VTA pathway.

36. **Adult hippocampal neurogenesis affects behavioral responses to an operant model of frustrative nonreward**. Mumeko C Tsuda, Rose-Marie Karlsson, and Heather A Cameron. Section on Neuroplasticity, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA. A common characteristic of several psychiatric disorders is irritability, which is defined as aberrant responses to frustration, or the absence of an expected reward. The hippocampus has been implicated in response to frustration. The present study investigated the role of adult hippocampal neurogenesis in behavioral responses to frustration induced by loss of an expected reward. We used valganciclovir to inhibit adult neurogenesis in male mice expressing the herpes simplex virus thymidine kinase (TK) under a GFAP promoter. Both TK and wild-type (WT) littermate controls were mildly food restricted and trained in operant chambers to lever press for food tablets on fixed ratio (FR) schedule where a light cue above the lever was paired with the reward. A progressive ratio (PR) test followed FR, and mice that reached 150 lever presses in the PR either received (rewarded group) or did not receive (frustrated group) a reward. Mice in both groups were shown the light cue associated with reward. After the PR, mice remained in the operant box for an additional 10 min where lever pressing had no scheduled consequence. Immediately after the 10 min period, mice were tested in the resident-intruder test of aggression. A negative control group spent time in the operant chamber but did not receive light cues or rewards during FR and PR. WT mice exposed to the frustration condition showed greater lever pressing and greater aggression relative to rewarded mice. Frustrated TK mice showed even greater lever pressing than WT mice in the same condition but showed baseline levels of aggression. These results suggest that adult hippocampal neurogenesis affects behavioral responses to frustration induced by the loss of an expected reward.

37. **Sexual hormones are not sufficient to achieve high sexual receptivity in female mice, sexual experience is required.** Sexual hormones are not sufficient to achieve high sexual receptivity in female mice, sexual experience is required. P. Marco-Manclús, W. Portillo, RG. Paredes Sexually naïve females mice show low levels of sexual receptivity evaluated by the lordosis reflex in their first sexual experience. Is not until 5th mating session that female mice show high levels of lordosis. Neuronal plastic mechanism involved in this process are not well understood. The aim of the study was to evaluate if higher doses of estradiol (E) and progesterone (P)are sufficient to increase sexual receptivity, and also to find out if sexual experience induces changes in the neuronal activity evaluated by the expression of early gen c- Fos in the Olfactory bulb, the Medial Preoptic Area, the Ventromedial Hypothalamus, the Bed nucleus of the Stria Terminalis and the Amygdala. To achieve this goal, CF1 ovariectomized female mice were assigned to one of the following groups: Experienced females (n=20), which received 6 mating sessions; Unexperienced females (n=18), which receive only 1 session; and Naïve females (n=18), which had no previous sexual experience; and a group treated with high doses of hormones (n=6). Females were hormonally primed with 1 µg of E and 100 µg of P (48h and 4h respectively, before the test), except for the high dose group which receive 10 µg of E and 1

mg of P. Each group was divided in 3 other subgroups: Mating group, which receive an extra mating session; Olfaction group, which was exposed to bedding impregnated with male sexually relevant odors; and Control group, which was exposed to clean bedding. 90 min after the test, animals were perfused, and their brains were coronally sliced. Our behavioral results showed that females increase their LQ (number of lordosis displayed/number of mounts) with repeated testing, and in first session of the high dose group the LQ was low and indistinguishable from the other groups (p=0.457). Preliminary immunhistochemical results for c-Fos detection show no difference in the c-Fos expression of the studied areas. Despite the fact that receptivity is hormo-dependent, hormones are not sufficient to increase sexual receptivity, sexual experience is required. A sexually experience probably did not involve and increase in the c-Fos expression. This research was supported by grants CONACYT 252756, 167101; Fronteras 374; UNAMDGAPA- PAPPIT IN203615, IN210215. We thank Francisco Camacho and Deisy Gasca for their technical assistance.

38. **New neurons promote behavioral recovery and structural plasticity following a rat model of post-traumatic stress disorder.** Timothy Schoenfeld1, Diane Rhee1, Laura Martin1, Heather Cameron1. 1Section on Neuroplasticity, National Institute of Mental Health. The hippocampus has been implicated in post-traumatic stress disorder (PTSD), as hippocampal volume loss is often found with patients suffering from PTSD and the hippocampus is known to be highly plastic in response to stress. One aspect of structural plasticity, adult neurogenesis, occurs robustly in the dentate gyrus region of the hippocampus and is highly regulated by stressful experiences. New neurons in the hippocampus are functionally important for normal regulation of the hypothalamicpituitary-adrenal (HPA) axis response to stress and animals without adult neurogenesis are more susceptible to behavioral change following acute stress. Therefore, we tested whether new neurons in the hippocampus were functionally important for behavioral and structural changes associated with traumatic stress. We used wildtype (WT) and GFAPTK (TK) transgenic rats treated with valganciclovir to inhibit adult neurogenesis for 8 weeks. Both WT and TK rats underwent a single-prolonged stress (SPS) procedure, a rodent model of PTSD which has delayed and long-lasting effects on learning, memory, and affect. Control and stressed rats were tested on a variety of behavioral tasks at different time points following SPS to determine the time course of behavioral change following traumatic stress, and were perfused to analyze the hippocampus for adult neurogenesis and volume changes. Two weeks following SPS, stressed WT rats show reduced neurogenesis in the dentate gyrus compared to non-stressed controls, and both stressed WT and TK rats display increased anxiety-like behavior, decreased spatial memory, and prolonged extinction of contextual fear memory compared to WT and TK controls. At this time point, only WT stressed rats display volume reduction, located in ventral portions of CA1. Six weeks following SPS, stressed WT rats have normalized levels of neurogenesis, no longer show hippocampal volume loss, and their anxiety-like behavior returns to baseline. However, at this same time point, stressed TK rats continue to have increased anxiety-like behavior and decreased spatial memory, The data suggest that new neurons are functionally important for behavioral normalization over time following traumatic stress.

39. **Persistent effects of acute stress on fear and drug-seeking in a novel model of the comorbidity between post-traumatic stress disorder and addiction.** Pizzimenti, Christie L1; Navis, Thomas M1 & Lattal, Matthew K1. 1Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, OR USA. Fear-related disorders and substance use disorders are highly comorbid. Even

following long periods of abstinence, comorbid individuals have high rates of relapse to drugs of abuse, especially in response to cues previously paired with drug. Previous attempts to characterize the role of fear on reinstatement have administered both the drug and the stressor within the same environment. Therefore, little is known about how fearful experiences in a specific context cause persistent changes in drug-seeking behavior in other contexts. To address this we assessed the effects of massive footshock in one context on drug seeking in another context using intravenous self-administration of methamphetamine in rats and cocaine-induced conditioned place preference in mice. Hyper-responsiveness to a mild stressor was assessed using a stress-enhanced fear learning procedure. Plasma levels of corticosterone (CORT) following footshock as well as following a dexamethasone (DEX) test were assessed using a radioimmunoassay to determine the role of hypothalamic-pituitary-adrenal (HPA) dysfunction in long-term stress effects. Mice with a history of footshock in a distinct context showed a significantly enhanced cocaine-induced place preference. In addition, massive footshock in a distinct environment produced long-term enhancements in cue-induced reinstatement of drug-seeking behavior in rats. These animals were also resistant to extinction following reinstatement. Although massive footshock produced an acute increase in CORT this change did not persist over time, consistent with reports in humans with post-traumatic stress disorder that cortisol levels are not chronically elevated. These studies demonstrate that a history of acute trauma leads to persistent changes in fear and drug-seeking behavior in other contexts, which mirrors aspects of the comorbidity between post-traumatic stress disorder and substance use disorders. These behavioral approaches provide a novel procedure for investigating basic mechanisms underlying this comorbidity and they provide powerful tools for testing preclinical pharmacological and behavioral interventions.

40. **Comparing the antidepressant efficacy of voluntary running and fluoxetine in a rat model of postpartum depression: effects on maternal care, depressive-like behavior, and hippocampal neurogenesis**. Gobinath, A.R.1, Richardson, R.J.2, Chow, C2, Workman, J.L.2, Lieblich, S.E.2, Barr, A.M.3, Galea, L.A.M1,2. 1Program in Neuroscience, University of British Columbia, 2Department of Psychology, University of British Columbia, 3Department of Anesthesiology, Pharmacology, and Therapeutics, University of British Columbia. Postpartum depression (PPD) affects approximately 15% of mothers and imposes a lifelong burden of mental health concerns for women. Pharmacological antidepressants such as fluoxetine (Prozac) are commonly used to treat PPD. However, use of fluoxetine during the postpartum period remains controversial due to concerns of efficacy as well as neonatal exposure to the drug. For this reason, non-pharmacological therapies such as exercise may be of interest as an alternative intervention. However, physiological changes that are characteristic of the postpartum period may alter the antidepressant potential of exercise and/or SSRIs (selective serotonin reuptake inhibitors). To investigate this, we treated rat dams daily with high levels of corticosterone (40 mg/kg), to induce a depressive-like phenotype, or oil during the postpartum period. Within the oil and corticosterone conditions, four additional antidepressant groups were created: 1. Fluoxetine (Prozac; 10 mg/kg) + exercise (voluntary access to running wheel); 2. Fluoxetine + no exercise; 3. Saline (vehicle for fluoxetine) + exercise; 4. Saline + No exercise. Dams were tested for alterations in maternal behavior and depressive-like behavior (forced swim test). We also quantified serum corticosterone levels as well as doublecortin (marker of immature neurons) expression in dorsal and ventral dentate gyrus. Daily running activity was recorded and using a median split, dams were further categorized as “high-running” or “low-running.” Preliminary results reveal

that maternal fluoxetine reversed corticosterone-induced disruptions in maternal care, especially in low-running but not high-running dams. Exercise also tended to decrease immobility (depressive-like behavior) in the forced swim test. The combination of exercise and fluoxetine attenuated stress-induced rises in serum corticosterone in comparison to fluoxetine alone. Finally, exercise bolstered doublecortin expression in ventral but not dorsal dentate gyrus in comparison to non-exercising dams. Of corticosterone-treated dams, the combination of high-running and fluoxetine increased doublecortin expression in ventral dentate gyrus in comparison to fluoxetine alone. Our findings show that maternal antidepressant treatments (Prozac, exercise) interact to differentially affect the well-being of the mother at the behavioral, endocrine, and hippocampal levels. Funded by CIHR to LAMG.

41. **Embracing nature's social network: The effect of an engaging environment on social responsiveness and oxytocin-immunoreactivity.** Neal, S.1, Kent, M.1, Bardi, M.1, Scarola, S.1, Perdomo, J.1, Thompson, B., Lambert, S.2, Lambert, K3. 1Randolph-Macon College, 2Furman University, 3Universty of Richmond. In contemporary society, there is an increased use of virtual reality in which humans are spending an inordinate amount of time interacting with screens as opposed to more naturalistic physical environmental stimuli consistent with the experiences of our ancestors. In 2016, for example, Facebook reported 1.5 billion monthly active users. Further, with the increased use of social media platforms, actual social interaction and engagement are also diminishing. Accordingly, in the current study, the effect of varying levels of environmental engagement on social responsiveness was investigated. Specifically, male Long-Evans rats were exposed to one of three environments: 1) group-housed in a naturally enriched environment (EE), 2) group-housed in a standard laboratory environment, or 3) housed in isolation in a standard laboratory environment (n=8). Previous work in the Randolph-Macon Behavioral Neuroscience Laboratory indicated that natural-enriched habitats promoted more social engagement than the artificial-enriched environment; thus, the natural-enriched environment was used. During the 4 weeks of assigned habitat exposure, spontaneous behavior was observed for 1 hour during the dark period for the social-housed groups. Also, each rat was assessed in a social responsiveness task. Following behavioral assessments, animals were perfused and brains were processed for oxytocin (OT) immunoreactivity in the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus and the medial forebrain bundle (MFB). Results indicated that, during dark-phase spontaneous behavioral observations, rats housed in EE displayed significantly higher rates of affiliative social behavior (i.e., active social contact, inter-male grooming and rough-and-tumble play) than the standard group-housed animals ($p=0.001$). However, higher rates of self-focused behavior (i.e., self-grooming) were observed in the standard group-housed rats ($p=0.03$). In the social responsiveness task, rats in EE directed more attention toward the novel conspecific in a restraint tube than the other two groups. For example, EE animals exhibited longer periods of sniffing bouts directed towards novel conspecific than the control ($p=0.006$). Results from neural quantification of OT-immunoreactivity indicated higher immunoreactive areas in the SON, but not in the PVN or the MFB, in the EE group ($p=0.04$). These findings suggest that environments promoting affiliative behavior enhance the responsiveness to novel conspecifics, potentially mediated by altered OT responsivity.

42. **Elucidating the neural circuitry of Social Familiarity induced Anxiolysis (SoFiA)**. S. Majumdar1,2, E.Lungwitz1,2, N.Bharadwaj3, K.Andrews2,4, A.Dietrich1,2, W.Truitt1,2. 1ANATOMY & CELL BIOLOGY, 2STARK NEUROSCIENCES RESEARCH INSTITUTE, 3CELLULAR & INTEGRATIVE PHYSIOLOGY, 4INDIANA

UNIVERSITY SCHOOL OF MEDICINE, INDIANAPOLIS, IN (NIH 1RO1MH106568). Mental health is crucially linked to social behavior. A crucial aspect of healthy social behavior involves learning to adapt emotional responses to social cues, for example learning to suppress anxiety through social familiarity, or social familiarity-induced anxiolysis (SoFiA). SoFiA is well documented and forms the basis of interpersonal therapies, however, the neural mechanisms of SoFiA are unclear. SoFiA is modeled in rats by employing social interaction habituation (SI-hab) protocol. Using SI-hab protocol it has been determined that SoFiA is a form of safety learning, requires both anxiogenic stimulus and social familiarity during training sessions and is dependent on the ventro-medial prefrontal cortex (vmPFC). Based on these findings we hypothesize that unique systems process anxiety and social familiarity signals and repeated convergence of these signals interact within the vmPFC to induce plasticity resulting in safety learning and anxiolysis. Here, as a first step towards investigating this hypothesis, we investigate putative molecular mechanisms and circuitry involved with SoFiA. Briefly, anxiety-like behavior was determined [via the social interaction (SI) test] using SI-hab protocol, which is a series of 5 daily 5-min SI tests. Here social familiarity (+/- SF) and anxiety (+/-Anx) during each SI-session was controlled, resulting in four groups: 1. Control (-SF/-Anx); 2. Social memory (+SF/-Anx); 3. Anxiety (-SF/+Anx); 4. SoFiA (+SF/+Anx). Behaviorally, groups 1 & 2 (Anx-) displayed no changes in SI time across all sessions, indicating no change in anxiety-like behavior. Comparatively, groups 3&4 (Anx+) had significantly reduced SI times. This anxiety-like response was overridden with SF (group 4). In group 4, SI times, compared to day 1 were sig increased on 4th and 5th session. Following the 5th session, rats were either sacrificed 30 min (n= 8/group for use in NARG analysis) or perfused 90 (n=8-10/group, for use in cFos analysis) min after SI. To gain insights into the molecular mechanisms of SoFiA response we identified a molecular activation signature in the vmPFC in groups 1-4. This was done with qRT-PCR analysis using our novel Neural Activity Regulated Gene (NARG) expression assay. Here, expression of 36 genes, which are known to be regulated by neural activity, were simultaneously determined and expression patterns identified. Both Anx and SF resulted in main effects of NARG expression, but the expression of a greater number of NARG was significantly affected by the SFxAnx interaction. Molecular activity signatures determined by clusters of gene expression patterns unique for SF, Anx and SFxAnx, are presented and discussed in relation to behavior. Additionally, cFos protein expression patterns were investigated in several brain regions that coincide with SF, Anx or SFxAnx main effects.

43. **The effects of JC3 on carrageenan/kaolin induced knee arthritis in rats**. Bongjun Sur1, Seikwan Oh1. 1Department of Molecular Medicine, TIDRC, School of Medicine, Ewha Women's University, Seoul, Korea. Yakuchinone B (JC6) and related enones showed several significant biological activities such as anti-inflammatory, antitumor, antibacterial, antiviral, and gastric protective activities. benzylideneacetophenone analog (JC3) was designed and synthesized based on a structural modification of yakuchinone B (JC6) in an effort to develop neuroprotective agents with beneficial effects in neurodegenerative diseases. In this study, anti-inflammatory effects of JC3 were investigated in the rats with 5% carrageenan/kaolin-induced knee arthritis. The arthritic symptoms of monoarthritic rats were evaluated by measuring knee thickness, squeaking score, weight distribution ratio, histological changes on knee joint, and serum Matrix metalloproteinase (MMP)-1 and Tumor necrosis factor (TNF)-α levels. At the maximum severity of arthritis, the daily treatment of JC3 was initiated and lasted for 6 days. The therapeutic effects of JC3 were observed on 6th day after the arthritis induction, as compared to saline-treated control group. JC3 significantly alleviated apparent

symptoms of arthritis. For histological analysis, rats were sacrificed on day 6 after experiment. The knee tissue fixed in the 10 % formalin, embedded into paraffin, sectioned, stained with hematoxylin-eosin solution, and examined by light microscopy for histological evaluation. JC3 also significantly reduced the symptoms of arthritis. In conclusion, JC3 was found to be effective in alleviating the arthritic symptoms in 5% carrageenan/kaolin-induced arthritic rats.

44. **The role of astrocyte DISC1 in cognitive behaviors**. Terrillion, C.E.1, Crawford, J.A.1, Shevelkin, A.1, Kim, S.H.1, Fukudome, D.1, Sawa, A.1, Kamiya, A.1, and Pletnikov, M.V.1. 1 Johns Hopkins University. DISC1 has been identified as a genetic risk factor associated with major psychiatric disorders, including schizophrenia, and is expressed in both neurons and astrocytes. Neuronal Disc1 in the hippocampus and the prefrontal cortex has been implicated in cognitive function. However, the role of Disc1 in astrocytes, which have increasingly been shown to play a role in normal cognition, has not been evaluated. We hypothesized that decreased expression of DISC1 in astrocytes in the hippocampus or prefrontal cortex would impair cognitive behavior in mice. Mice were injected with the vector AAV1-GFAP::GFP-miR30-DISC1 (Disc1 KD) in the hippocampus or prefrontal cortex (PFC) to knock down DISC1 in astrocytes, or the scrambled control vector AAV1-GFAP::GFP-mir30-Ctrl (Ctrl). 2 weeks following injections, mice were tested in anxiety related measures including elevated plus maze and the open field, as well as several complex cognitive behaviors, including, social interaction, Barnes maze and trace fear conditioning. Gene expression and astrocyte morphology was assessed in the mouse brain following behavioral experiments. DISC1 KD in hippocampal astrocytes did not alter locomotor activity or anxiety related behavior but significantly decreased social preference and reduced preference for a novel mouse in the social interaction test. Additionally, DISC1 KD in hippocampal astrocytes impaired performance in the Barnes maze and reduced cue-dependent freezing in in trace fear conditioning. While DISC1 KD in PFC astrocytes also impaired performance in the Barnes maze, no significant effects of this KD were observed on cue-dependent freezing in trace fear conditioning. We found that DISC1 KD altered astrocyte morphology through increased branch diameter. Reduction of DISC1 expression in brain astrocytes leads to brain region-dependent deficiencies in complex cognitive tasks. Changes in astrocyte morphology following DISC1 KD suggests that astrocytic dysfunction likely contributes to the cognitive deficits. Further understanding of the role DISC1 has in astrocyte function in relation to cognitive behaviors will allow us to improve treatment of cognitive symptoms in patients with major psychiatric disorders.

45. **Orexin modulates synaptic transmission in the central vestibular system.** Y Jiang1, TF Lam1, CW Ma1, DKY Shum1, JJ Wang2, YS Chan1. 1School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, 2Department of Biological Science, Nanjing University, Nanjing, China. Orexin is known to modulate synaptic plasticity in the hippocampus and contribute to social memory in adult rodents. While orexinergic neurons in the lateral hypothalamus project to the vestibular nucleus (VN), the role of orexin in the maturation of vestibular functions remains unexplored. We hypothesized that orexin modulates synaptic transmission in the VN, thereby regulating the expression of vestibular-related behaviors during postnatal development. Our immunohistochemical results showed that orexin receptors and orexin-immunopositive neurons are present in the VN. Also, pharmacological perturbation of orexin receptors in the VN of neonatal rats led to impairment in developmental acquisition of vestibular-related behaviors such as air-righting reflex. To understand the role of orexin on synaptic transmission in the VN, we employed in vitro

whole-cell patch-clamp technique to study the action of orexin on the excitability of neurons in the medial vestibular nucleus (MVN) of rats at postnatal day 14. Treatment with orexin led to reduction in amplitude and frequency of miniature inhibitory postsynaptic current (mIPSC). This suggests that orexin decreases both presynaptic release of inhibitory transmitters and postsynaptic depolarization within the MVN. Notably, we found that agonist of orexin 2 receptor reduced the frequency but not amplitude of mIPSC. We have thus demonstrated that orexin suppresses synaptic inhibition on MVN neurons. We further investigated whether orexin-modulated mIPSC is mediated by GABA-A receptors or glycine receptors. With the use of bicuculline and strychnine, we observed that orexin decreased mIPSC mediated by GABA-A receptors, but not glycine receptors. Taken together, our findings provide us with fundamental knowledge about the modulatory role of orexin in GABAergic transmission within the VN and its impact on postnatal refinement of neural circuit for vestibular-related behavior. [Supported by N_HKU735/14].

46. **Early life stress can elicit some Schizophrenia-like symptoms in the dopamine transporter heterozygous mice**. David Groenewoud1, Leanne Mak Hui Min2, Toh Jia Min1, Peiyan Wong2. 1Department of Biological Sciences, National University of Singapore. 2Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore. Schizophrenia is a disorder with complex aetiologies. Based on the two-hit hypothesis of schizophrenia, genetic factors cause a disruption of the early central nervous system development. These early disruptions result in long-term vulnerability to a “second hit” that then leads to the onset of schizophrenia symptoms. However, current animal models for schizophrenia do not explicitly integrate genetic factors with environmental factors. One such established animal model for schizophrenia is the dopamine transporter (DAT) knockout mice. These mice have a hyperdopaminergic tone and exhibit endophenotypes that recapitulate positive symptoms of schizophrenia, including hyperlocomotion, stereotypy, sensorimotor gating deficits and cognitive impairments. Whereas their heterozygote (HT) counterparts are behaviourally similar to wild-type mice, even though they have reduced levels of DAT. Here, we investigate whether an early life stressor, such as maternal separation, when applied to the DAT heterozygotes, will elicit schizophrenia-like behaviours in young adulthood. Litters assigned to the maternal separation (MS) group were separated from the dams for 3 hours per day, from postnatal day 1 to day 14. This took place between 09:00 and 15:00 h. Litters in the control group were left undisturbed throughout the experiment. At the end of the procedure, all litters remained undisturbed until weaning at 3 weeks, and behavioural testing started at 8 weeks of age. Anxiety-like behaviours and exploratory activity were respectively assessed with elevated zero maze and light-dark box, and the open-field test. Cognitive function was assessed in the novel object recognition and social transmission of food preference paradigms. Sensorimotor gating was evaluated using the prepulse inhibition of acoustic startle (PPI) paradigm. In the tests for anxiety-like behaviours, we found that MS DAT HT mice behaved similar to non-MS controls in the light-dark box. In the zero maze, MS DAT HT mice showed an increased number of transitions between the open arms and have a somewhat increased exploratory time in the open arms compared to controls. We found that the locomotor activity of MS DAT HT mice was reduced in the open field test compared to controls. In the cognitive tests, MS DAT HT mice showed impaired episodic memory in the novel object recognition test compared to controls. However, MS did not affect cognitive function in the social transmission of food preference test. The PPI test showed that MS DAT HT mice have deficits in sensorimotor gating compared to non-MS controls. Overall, our findings suggest that maternal separation caused DAT HT

mice to exhibit increased schizophrenia-like behaviours like that of their KO counterparts in certain domains, such as in episodic memory and sensorimotor gating. Whereas other behavioural domains such as anxiety-like behaviours, remain mostly unaffected by MS.

47. **Representation of delay discounting in hippocampus and medial prefrontal cortex**. Masuda, Akira1; Sano, Chie1; Fujisawa, Shigeyoshi2; Itohara, Shigeyoshi1. Lab for Behavioral Genetics1, Lab for Systems Neurophysiology2, BSI, RIKEN, Wako-shi, Saitama, Japan. Impulsivity is a major characteristic of patients with drug abuse and psychological disorders. Dysfunctions of the medial prefrontal cortex (mPFC) and hippocampus can lead impulse control disorders, characterized by mistimed actions or decisions without due consideration of their consequences. However, it is not well known the relationships between activities of these brain regions. Here, we recorded the activities of single neurons in hippocampal CA1 and mPFC, of mice performing a delay-based decision-making task in a T-maze. Large and small rewards were allocated to each side arm with or without a delay, respectively. The delay length in the large-reward arm was progressively increased in each block (0, 5, 10, 20 and 40 s) in each session. The choice ratio to the large reward-delayed arm was negatively correlated with the delay durations. Putative excitatory and inhibitory neurons were identified by cell type classification with waveform parameters. Sizable amount of CA1 and mPFC excitatory neurons showed significant increases (about 40% of the population) in their firing rates during long (>20 s) delay periods. Next, we investigated the place-dependency of the delay-activated neurons by switching the large reward-delayed arm with the small reward-non-delayed arm. Numerous (about 70 %) delay-activated neurons found in CA1 were location selective (neurons specifically fired on one side) whereas few delay-activated neurons in mPFC (30 %) were location selective. Firing rate was decreased in CA1 but more widely varied in mPFC by changing reward size 4 to 1. This suggests firing in CA1 excitatory neurons during delay reflect reward expectation whereas that in mPFC reflect both reward expectation and negative emotion including delay-induced stress. Our findings indicate that mPFC neurons encode the information for discounting reward values by a delay and that hippocampal neurons encode the integrated information for value, positions and delay. Grant/Other Support: : JSPS KAKENHI Grant 16K15196.

48. Prebiotic-mediated changes in attention in healthy human population. Attila Tóth[1], Zhinoo Amiri[2], Zoltán Vizvari[4], Kitti Mintál[5], László Lénárd[1], Zoltán Karádi[1], Renáta Cserjési[3]. [1]Institute of Physology, Pécs University, Medical School, Pécs, Hungary. [2]Institute of Psychology, Student Eötvös Loránd University, Department of Clinical Psychology, Budapest, Hungary. [3]Institute of Psychology, Eötvös Loránd University, Department of Affective Psychology, Budapest, Hungary. [4]Institute of Electronics, Pécs University, Faculty of Engineering, Pécs, Hungary. [5]Institute of Biology, Student Pécs University, Faculty of Sciences, Pécs, Hungary. In the last century people's lifestyle has dramatically changed, and the shift away from traditional lifestyles has caused the increase in mental disorders. The gut-brain axis consists of bidirectional communication between the central and the enteric nervous systems. Recent evidence, mainly arising from animal models, supports a role of microbes as signaling components in the gut-brain axis. Diet has recently been shown to contribute to both physical and mental disorders as a risk factor, because there is strong relationship between diet and intestinal microbiota, which are important in normal healthy brain function. Rodent studies demonstrating neurobiological changes following special (pre- and probiotic) diet intake revealed its significant benefits in antiinflammatory and neuroprotective actions. In addition, some data did show robust and

well defined effects of prebiotics on several behavioral paradigms, such as anxiety, learning, and memory. Evidence for cognitive deficits have now been identified in numerous intestinal and extraintestinal diseases (Autism, ADHD, anxiety, irritable bowel syndrome, inflammatory bowel disease, coeliac disease). The aim of the present study was to quantify the organismic changes in whole body composition by means of bioimpedance measurements, and those of cognitive function after 2 weeks of special diet period. These goals have been achieved by employing a new impedance measuring equipment and standard cognitive tests including Stroop, Attentional Network, and Digit span tests. Student volunteers (n=24, 15 female) were randomly divided into two groups: the control (all food allowed but those that have been recommended to diet group) and diet (list of special food ingredients) ones. At the baseline, diet and control groups did not differ in terms of initial weight, eating habits, level of eating problems, and mood. Impedance result was associated with the composition and ratio of total body fat, and in female volunteers, the menstrual cycle as well. Although this time only marginal effects were revealed concerning interrelation of diet and cognitive behavioral actions (the p value was at p=0.07), it is worth noting that there was a slight diet effect on the attention capacity change when gender was included as co-variate. Furthermore, there was an interaction between working memory capacity and diet type. The preliminary results indicate the positive effects of diet in attention and working memory, and its capacity to also influence body composition.

49. **Testing the influence of different conditions on passive and active fear responses in a shock-based avoidance paradigm: behavioral and circuit analysis**. Viellard J. 1,2, Herry C.2, Canteras N.S.1. 1Anatomy department of the Institute of Biomedical Science, Laboratory of Functional neuroanatomy, University of São Paulo, São Paulo, Brazil; 2Neurocentre Magendie INSERM U862, Laboratory of Physiopathology of neuronal plasticity, University of Bordeaux, Bordeaux, France. e-mail: j.viellard@usp.br. It is well known that the spatial location of an individual towards a potential threat determines the nature of the fear response. Depending on the proximity of the threat, an individual may display a freezing, avoidance or a fight response. Our group has investigated a non-instrumental avoidance paradigm, where the individual learn to avoid a threaten-associated environment using contextual cues. In a previous study (Viellard et al. 2016), we showed in rats that testing conditions in shock-based contextual fear conditioning influence both the behavioral responses and the activation of circuits potentially involved in contextual avoidance. In the present work, we validated the same model in mice, and tested shock-based contextual fear responses using two different behavioral testing conditions: confining the animal in the conditioning chamber or placing the animal in an apparatus with free access to the conditioning compartment. Our results showed that during the contextual fear test, the animals confined to the shock chamber exhibited significantly more freezing. In contrast, the animals that could avoid the conditioning compartment displayed almost no freezing and exhibited risk assessment responses. The animals that were able to avoid the shock chamber presented increased Fos expression in the juxtadorsomedial lateral hypothalamic area, the dorsomedial part of the dorsal premammillary nucleus and the lateral and dorsomedial parts of the periaqueductal gray, which are elements of a septo/hippocampal–hypothalamic–brainstem circuit that is putatively involved in mediating contextual avoidance.Validating these results in mice helped us outline a circuit, which may be tested on functional grounds using optogenetic tools to investigate its role on contextual fear responses. Financial support: FAPESP n. 2016/08640-7 ; 2014/05432-9.

50. **The quality of the living environment affects the fluoxetine treatment outcome**. S. Poggini1, A.Viglione1, G. Matte Bon1, S. Alboni2, S. Garofalo3, L. Maggi3, I. Branchi1,4. 1PhD Program in Behavioral Neuroscience, Sapienza University of Rome, ITALY. 2University of Modena and Reggio Emilia, Department of Life Sciences, Modena, Italy. 3Sapienza University of Rome, Department of Physiology and Pharmacology, Rome, Italy. 4University of Zurich, Istitute of Anatomy, Zurich, Switzerland. Selective serotonin reuptake inhibitors (SSRIs) are the most common pharmacological treatment for Major Depression. It has been hypothesized that these drugs affect mood through changes in immune function. However, findings concerning the SSRI effects on inflammation are contradictory showing that these drugs act either as pro- or anti-inflammatory compounds. Since previous studies showed that SSRI effects are moderated by the quality of the living environment, we investigated whether the environment determines the effects of SSRI treatment on behavior and inflammation. We treated C57BL/6 adult male mice with either fluoxetine or vehicle while exposing them to either an enriched or a stressful condition, following a chronic stress period aimed at inducing a depression-like phenotype. We measured the most commonly investigated behavioral endophenotypes of depression and SSRI outcome, including liking- and wanting-type anhedonia, cognitive bias, BDNF and corticosterone levels. In addition, in the whole hippocampus, we assessed expression levels of pro- and anti-inflammatory cytokines. In isolated microglia, we performed RT-PCR to assess the expression levels of a number of pro- and anti-inflammatory-related genes. The treatment affected the investigated neurobehavioral endpoints according to the quality of the living environment. In particular, mice treated with fluoxetine in an enriched condition overall improved their depression-like phenotype compared with controls, whereas those treated in a stressful condition showed a distinct worsening. In addition, fluoxetine treated mice exposed to enrichment showed increased expression of pro-inflammatory cytokines and decreased expression of anti-inflammatory-related genes. Whereas, mice treated while exposed to stress showed the opposite profile. In particular, a decrease in pro- and an increase in anti-inflammatory cytokine expression both in the whole hippocampus and isolated microglia. Our results indicate that the effects of SSRI treatment depend on the quality of the environment, providing a possible explanation for the inter-individual differences in SSRI action and effects. These findings may allow for a more effective personalization of antidepressant treatment strategies based on the quality of the living environment of the depressed patient. Supported by the Italian Ministry Of Health, RF-2011-02349921, The role of the brain-adipocyte axis activity in potentiating antidepressant efficacy.

51. **Seizuring and cognitive long-term effects of a bad first-line antiepileptic treatment choice on the following-line treatment efficacy in a mouse model of absence epilepsy**. Hadjadj Sarah3, Kuchenbuch Mathieu3,4, Dieuset Gabriel1,2, Costet Nathalie1,2, Biraben Arnaud1,2,5. Martin Benoît1,2 1INSERM, U1099, 35000 Rennes, France, 2Université de Rennes 1, Laboratoire de Traitement du Signal et de l'Image (LTSI), 35000 Rennes, France, 3Département de Neurologie Pédiatrique, CHU Rennes - hôpital sud, 35203 Rennes, France, 4Département des Explorations Fonctionnelles Neurologiques, CHU de Rennes-Pontchaillou, 35000 Rennes, France, 5Département de Neurologie, CHU de Rennes-Pontchaillou, 35000 Rennes, France. Possible aggravation of epilepsy by antiepileptic drugs is an already known phenomenon. Overdoses and drug interactions are the two main reasons. However, seizures can also be worsened because of an inadequate treatment. This is often the case for children epilepsies such as childhood absence epilepsy. In a previous study, we

addressed the problem of whether an inadequate first-line treatment could abolish the efficacy of a second-line treatment that would have been successful if applied as a first-line treatment. We used an inbred mouse model for absence epilepsy, BS/Orl, manifesting spontaneous and recurrent spike-wave discharges. Mice were submitted to an experimental protocol where they received two consecutive treatments. From the age of five weeks, mice were given valproate (VPA - reference), vigabatrin (VGB - known to aggravate the absence epilepsies) or ethosuximide (ESM - a specific for absence epilepsies) during 14 days. And then, they all received VPA during 42 days. A fourth group has received a saline solution (PHY) during the whole experiment. The 4 groups were assessed at 5 different times: before any treatment, after the first-line treatment and 3 times during the second-line treatment. After the first-line treatment, the 3 groups VPA, VGB and ESM were differing significantly as expected: compared to PHY, VGB was found to worse seizures whereas VPA and ESM were found to reduce seizures with a much greater effect for ESM. Interestingly, the application of the second treatment showed various effects. While the seizure level in the ESM group was much lower than in the VPA group after the fist-line treatment, this benefit has progressively disappeared with the introduction of the VPA. Finally, after 6 weeks of VPA treatments, both ESM-VPA and VPA-VPA were presenting the same seizure occurence rate. Conversely, while the VGB has aggravated the seizure level compared to the PHY group during the first-line treatment, the introduction of the VPA as the second treatment, has failed to reverse the tendency of an aggravation of the seizure level due to the initial application of the VGB. This study has shown that an inadequate first-line treatment, more than worsening seizures, can have long-term adverse effects by reducing the efficacy of a posterior treatment. In a second study, we hypothesized that the inadequate antiepileptic therapy may be also responsible for the cognitive impairment frequently observed with epilepsy, even if it was relayed by an appropriate antiepileptic treatment, and not only the seizuring intensity. We tested our hypothesis with the same model and the same protocol than for Study 1, except that we added carbamazepine (CBZ - known to aggravate the absence epilepsies such as VGB). We only found significant results (shuttle-box and plus-maze) with CBZ clearly suggesting that CBZ impairs learning abilities when prescribe inadequatly. The whole studies 1 and 2 are planned to be replicated in a more important study in duration and in number of anti-epileptic drugs to take into account the ones more frequently used in North-American and Europe.

52. **Bi-directional modulation of impulsive behavior by the subthalamic nucleus.** Lukasz Piszczek[1], Andreea Constantinescu[1], Anton Pekcec[2], Janet Nicholson[2] and Wulf Haubensak[1]. [1]Research Institute of Molecular Pathology (IMP), Vienna, Austria. [2]Department of CNS Diseases Research, Boehringer Ingelheim Pharma GmbH & Co. KG Biberach, Germany. Inhibitory control, an ability to suppress and cancel prepotent responses is a key element of cognitive control. Impairment in this function underlies both impulsive and compulsive behaviours, which are key traits of conditions such as: attention deficit/hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), as well as addiction. Maladaptive inhibitory control is highly correlated with increased trait impulsivity, a highly complex behavior, involving incentive salience, attention and fast action response. The subthalamic nucleus (STN) is a relatively small nucleus of the basal ganglia circuitry, which is known to play a major role in motor control. Furthermore, therapeutic effects of STN high frequency deep brain stimulation in both motor (such as Parkinson's disease) as well as nonmotor (obsessive compulsive disorder) diseases suggest its involvement, beyond motor control, in cognitive functions. Interestingly, there is increasing evidence associates STN activity with stopping abilities in impulsivity-

related tasks in human and animal subjects. Here, we investigated the role of the STN in impulsivity control. We combined the Go/No-Go task, a behavioral assay successfully applied in both humans and rodents, with optogenetic manipulation of STN activity. Optogenetic activation decreased, whereas optogenetic inhibition increased impulsive parameters, mimicking atomoxetine and amphetamine pharmacological effects, respectively. Finally, we took advantage of the temporal resolution of optogenetic manipulations, assigning a selective role of the STN in the anticipatory phase of the task rather than in cue-driven responses. Taken together, our study suggests that STN circuits might represent a novel biomedical target at a crossing point between motor and cognitive functions, outside the classical reward circuitry.

53. **Genetic background is a significant driver of Alzheimer's disease associated phenotypes.** Kristen D. Onos[1], Kelly J. Keezer[1], Casey J. Acklin[1], Harriet M. Jackson[1], Travis L. Cossette[1], Rita O'Rourke[1], Stacey J. Sukoff Rizzo[1] and Gareth R. Howell[1, 2] [1]The Jackson Laboratory, Bar Harbor, ME [2] Sackler School of Graduate Biomedical Sciences, Tufts University School of Medicine, Boston, MA. Alzheimer's disease (AD) pathology is characterized by accumulation of beta-amyloid plaques, neurofibrillary tangles of tau (NFT), marked neuroinflammation, and widespread neuronal loss. Current mouse models of AD have allowed researchers to make significant strides towards understanding the specific biology underlying the disease. However, these mouse models lack large-scale neurodegeneration, which is the major feature of human AD. Furthermore, efforts to assess behavioral and cognitive phenotypes in these models and to translate these findings in the patient have been unsuccessful. Most of these models have been developed exclusively on a single mouse background, C57BL/6J (B6), limiting genetic diversity. This is the equivalent of studying AD in a single patient, rather than being reflective of the diversity within the human population. To address this, our lab has created a genetically diverse panel of inbred mouse models by backcrossing the familial mutations in Amyloid Precursor Protein (APP^{swe}) and Presenilin 1 ($PS1^{de9}$) from the B6 background to the founder strains of the Collaborative Cross. This is the first time that wild-derived strains – CAST/EiJ, PWK/PhJ and WSB/EiJ– have ever been used to study AD. These strains show significant differences in associated AD-risk behaviors. Male and female animals (carriers vs. wild-type) were run through an extensive battery (with multiple measures) to assess metabolic and cognitive function. Histological and biochemical analyses of neuroinflammation, beta-amyloid, tau, and neuronal health show significant variation across strains, and attest to the importance of genetic background in improving translatability to human disease. These genetically diverse AD mouse models represent a unique resource to improve the biological underpinnings of AD, and lay the foundation for identifying novel therapeutic targets. Jane B. Cook Foundation JBC1983. Ruth L. Kirschstein Institutional National Research Service Award (T32)

FRIDAY, June 30

Keynote Speaker

08:00-09:00 **The female rat preoptic area contains discrete sets of efferent estrogen-sensitive neurons for proceptive or receptive component of sexual behavior.** Yasuo, Sakuma. *Setouchi Hall, Room 1-2*

The female rat preoptic area contains discrete sets of efferent estrogen-sensitive neurons for proceptive or receptive component of sexual behavior. Yasuo Sakuma, University of Tokyo Health Sciences, Tama, Tokyo 206-0033, Japan. Electrical stimulation of the preoptic area (POA) interrupts the lordosis reflex, the major receptive component of sexual behavior in female rat in estrus, without interfering with the proceptive component of sexual behavior or solicitation. Axon-sparing POA lesions with an excitotoxin, on the other hand, enhance lordosis and diminish proceptivity. The disruptive POA effect on the lordosis reflex is mediated by estrogen-sensitive POA projection to the ventral tegmental area (VTA) as shown by the behavioral effect of VTA stimulation as well as by the demonstration of an increased threshold for antidromic activation of POA neurons from the VTA in ovariectomized females treated with estradiol benzoate (EB). EB administration increased the antidromic activation threshold in ovariectomized females and neonatally castrated males, but not in neonatally androgenized females; i.e., the EB effect was present only in those that show lordosis in the presence of EB. EB causes behavioral disinhibition of lordosis through an inhibition of POA neurons with axons to the VTA, which eventually innervate medullospinal neurons innervating spinal motoneurons of the back muscle. Based on the results in GT1-7 cells, we concluded that the EB-induced change in the axonal excitability was due to EB-induced alterations in BK channel expression. Recordings from freely moving female rats engaging in sexual interactions revealed separate subpopulations of POA neurons for the receptive and proceptive behaviors. Those POA neurons engaging in the control of proceptivity are EB-sensitive and project to the midbrain locomotor region (MLR). EB-induced excitation of POA outputs to the MLR may culminate in an increased locomotion that embodies enhanced proceptivity in the female rat in estrus.

09:30-11:30 **Symposium: Overlapping neural mechanisms mediating substance abuse and depression.** Chair: Nii Addy. *Setouchi Hall, Room 1-2*

Overlapping ventral tegmental area cholinergic mechanisms mediating cue-induced drug-seeking and behavioral responses to stress and anxiety. Nii A. Addy1,2,3, Eric J. Nunes1, Keri M. Small1, Shannon Hughley1, Lillian Bitner4, and Sofia Walton1. 1Department of Psychiatry, 2Department of Cellular and Molecular Physiology, 3Interdepartmental Neuroscience Program, 4Department of Molecular, Cellular, and Developmental Biology. Yale University, New Haven, CT, USA. The role of ventral tegmental area (VTA) acetylcholine in substance abuse has historically been investigated in terms of cholinergic receptor mechanisms mediating drug reinforcement. We and others have shown that VTA cholinergic receptors also regulate phasic dopamine activity that has been critically linked to cue-induced drug-seeking and to responses to stress and anxiety. However, prior to the studies from our laboratory, the potential role of these VTA cholinergic mechanisms in response to stress and anxiety was unknown. Here, we sought to determine whether overlapping VTA cholinergic mechanisms mediate drug-seeking behavior as well as stress and anxiety-related behavior. First, we used an intravenous (i.v.) cocaine self-administration paradigm in male Sprague-Dawley rats that received 10 day self-administration training (~0.5 mg/kg/infusion cocaine delivery on an FR1 schedule), followed by 10 days of forced abstinence. We subsequently found that blockade of VTA nicotinic or muscarinic acetylcholine receptors (nAChRs or

mAChRs respectively) attenuated cue-induced cocaine-seeking on withdrawal day 10. In a separate experiments, we found that blockade of VTA mAChRs also decreased immobility time in the forced swim test (FST) and increased open arm time in the elevated plus maze (EPM) – consistent with antidepressant-like and anxiolytic-like effects. In additional experiments, we have found that 10 day cocaine self-administration followed by 2 week withdrawal induced an anxiogenic-like phenotype, as reflected by decreased open arm time in the EPM. Given the comorbidity between substance abuse and depression, we are currently determining whether VTA mAChR blockade is sufficient to reverse this cocaine-withdrawal induced anxiogenic effect. In other experiments, we are also identifying the specific mAChR subtype(s) mediating these behavioral effects and examining whether these effects are mediated via regulation of dopaminergic signaling. The findings from this work have important translational implications, given the possibility for mAChRs to serve as novel therapeutic targets to both limit drug-seeking and ameliorate depression and anxiety-related symptomology. This work was supported by National Institutes of Health (NIH) grants MH108663 (NAA and EJN), R25 GM104553 (SMH), and MH014276 (KMS).

Cacna1c (Cav1.2) as a candidate risk gene for the effects of stress on mood-related and cocaine-seeking behavior. Anjali M. Rajadhyaksha1,2, Charlotte C. Bavley1,2, Caitlin E. Burgdorf1,2. 1Feil Family Brain and Mind Research Institute, 2Pediatric Neurology, Pediatrics, Weill Cornell Medicine of Cornell University, NY, NY 10065. Genetic predisposition significantly influences susceptibility to stressful life events leading to mood disorders and substance abuse. Overlapping neurocircuitry and convergence of cellular and molecular mechanisms have been suggested to underlie the effects of stress on neuropsychiatric-related conditions. The CACNA1C gene that codes for the Cav1.2 subunit of the voltage-gated L-type Ca2+ channel, critical mediators of experience-dependent plasticity in the brain, has emerged as a significant candidate risk gene for multiple neuropsychiatric disorders, including bipolar disorder, schizophrenia, and major depressive disorder. Stressful events contribute to the manifestation of all these conditions that are also co-morbid with drug abuse. Deficits in the functional connectivity of the prefrontal cortex (PFC) have been associated with most neuropsychiatric disorders. The PFC is particularly susceptible to the effects of chronic stress, displaying changes in gene expression, dendritic spine morphology and synaptic plasticity. Additionally, human carriers of the risk-conferring single nucleotide polymorphisms (SNPs) in CACNA1C show alterations in PFC structure and function, suggesting a critical role of Cav1.2 in maintaining functionality of this region. Work from our lab has found that chronic stress increases Cav1.2 protein expression in the PFC and using genetic Cav1.2-deficient mice we find that Cav1.2 mediates the effects of chronic stress on depressive-like and anxiety-like behavior. Using focal conditional knockout of Cav1.2 in the PFC, we find that following extinction of cocaine place preference, Cav1.2 channels mediate stress-primed cocaine seeking behavior. Molecular studies have identified that Cav1.2-mediates chronic stress-induced activation of the p25/Cdk5/glucocorticoid receptor pathway in the PFC, a mechanism that may contribute to altered function of this brain region. These findings support human studies identifying the PFC as a susceptible region in CACNA1C disease risk carriers and that stress may contribute to the development of neuropsychiatric conditions via Cav1.2 mechanisms within the PFC. This work was supported by National Institutes of Health (NIH) grants RO1 DA029122 (AMR), The Hartwell Foundation (AMR), and Weill Cornell Autism Research Program (AMR).

Orexin's are mediators of vulnerability to the effects of stress. Seema Bhatnagar, Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine. Orexins are hypothalamic europeptides important in arousal and mediate anxietyrelated behavior, responses to stress and

sensitivity to drugs of abuse. We are interested in how orexins regulate habituation to repeated stress and mediate vulnerability to the effects of chronic social defeat. Our results indicate that elevated orexins contribute importantly to the reduced ability to adult female rats to habituate to repeated restraint stress and subsequent deficits in cognitive flexibility. In addition, orexins are elevated in adult male rats that exhibit vulnerability to the effects of chronic social defeat. The vulnerable phenotype includes increased anxiety-like and prodepressive behaviors along with disrupted hypothalamic pituitary adrenal function. Thus, orexins are likely to be important in the coupling of stress, anxiety and the behavioral changes that occur with drugs of abuse.

The CRF and Dynorphin systems in the central amygdala differentially control escalation of nicotine intake and negative emotional states. Olivier George. The Scripps Research Institute, Department of Neuroscience. 10550 N Torrey Pines Road, La Jolla, CA 92037. The mechanisms underlying the escalation of nicotine intake in dependent animals are largely unknown. Converging evidence suggest that recruitment of the corticotropin releasing factor (CRF) and dynorphin systems are a key factor in the development of disorders associated with increased stress level, including addiction. I will present preclinical data demonstrating the key role of the CRF-CRF1 and Dynorphin-KOR systems in animal models of nicotine addiction. Specifically, I will show electrophysiological, neuroanatomical and behavioral evidence that the CRF and Dynorphin systems control both nicotine intake during self-administration and the negative emotional states during withdrawal, but that the CRF and Dynorphin systems play different roles. The results show that nicotine dependence produces neuroadaptations leading to increased nicotine-induced GABA transmission onto CRF+ neurons and that blocking CRF1R reverses escalation of nicotine intake. On the other hand with observe a switch in the effect of KOR activation on GABA transmission (from inhibitory to stimulatory) and an upregulation of preprodynorphin levels in the CeA during nicotine withdrawal. Finally, downregulation of preprodynorphin levelsin the CeA using viral vectors prevents abstinence-induced hyperalgesia, aversion to nicotine withdrawal and stress-induced reinstatement of nicotine seeking but does not affect escalation of nicotine self-administration. These results demonstrate that CRF and Dynorphin systems control both nicotine intake during self-administration and the negative emotional states during withdrawal but that the CRF and Dynorphin systems play different roles. This talk will highlight both the overlapping and the divergent neuronal mechanisms of nicotine intake and nicotine withdrawal.

09:30-11:30 **Symposium: Pharmacological and environmental strategies to enhance cognition.** Chairs: Riccardo Brambilla and Lorenzo More. *Setouchi Hall, Room 6*

The role of Mitogen and Stress activated protein Kinase 1 in response to environmental enrichment, a possible target for nootropics? Lorenzo Morè1, Lucia Privitera1, Bruno Frenguelli1. 1University of Warwick, School of Life Sciences, Coventry UK. Mitogen and Stress activated protein Kinase 1 (MSK1) is a nuclear kinase downstream of BDNF-activated TrkB receptors and has the ability to regulate gene expression via the phosphorylation of both CREB at S133 and histone H3 at S10. Mice lacking the kinase activity of MSK1 do not display the enhancement of hippocampal synaptic transmission observed in wild-type mice after environmental enrichment (EE) and show an abnormal spine density, thus MSK1 places itself as a key component of the complex molecular machinery by which EE affects neuronal structure, synaptic function and ultimately cognition. Environmental enrichment has been known to provide enhanced learning and memory, greater resilience to stress, higher resistance to the addictive effects of drugs of abuse and improved recovery in both acquired and neurodegenerative brain injury. It is still unclear however to what extent each piece of the complex molecular machinery is involved in the

cognitive component of EE-induced adaptation. Our most recent work suggests that MSK1 is a major contributor in translating positive environmental experience into enduring forms of neuronal structural and functional modifications and into the enhanced cognition associated with enrichment. The major effects of EE we tested were on reducing anxiety and improved cognitive flexibility measured as reversal learning in a spatial navigation task. Interestingly the anxiolytic and associated motoric adaptations to EE were present in all groups while MSK1 kinase-dead mice fell shorter than wild-type in responding to EE by increasing their cognitive flexibility; thus MSK1 seems to be a key kinase underlying cognitive flexibility. Interestingly MSK1's role appears to be differentially important during the life of a mouse having its major effects in early and old age while it seemed less prominent in adult life. A pilot experiment using a sub-chronic treatment with a nootropic cast further evidence for a major role of MSK1 into translating cognitive enhancement; treated wild-type mice showed cognitive flexibility performance similar to EE-reared mice while kinase-dead did not. We argue that in virtue of its position within the nucleus, MSK1 might provide a more selective target for a nootropic to act on TrkB signalling transduction cascade. This work was funded by the BBSRC and WPH.

Strategies for countering spine defects and promoting learning in aging and developmental intellectual disability disorders: Ampakines and environmental enrichment. Julie Lauterborn1, Gary Lynch1,2, and Christine M. Gall1,3. Depts. of 1Anatomy & Neurobiology, 2Psychiatry and Human Behavior, and 3Neurobiology and Behavior, University of California at Irvine, USA. Dendritic spine abnormalities are thought to underlie learning and memory deficits, and are present in a variety of conditions including developmental disorders and aging. Consequently, therapeutic strategies that correct or prevent spine defects could potentially be useful for enhancing cognition and normalizing behavior. Ampakines are a class of nootropics that positively modulate AMPA-class glutamate receptors, promote neurotrophin (e.g., BDNF) expression, and facilitate both long-term potentiation and learning. While ampakines have been tested in animals and humans with positive results, only a few studies in rodents have begun to assess the long-term effects of treatment. Recently, we tested if daily ampakine treatment over 2.5 months could offset the deleterious effects of normal aging in rat on hippocampal neuronal morphology, synaptic plasticity, and behavior. To avoid possible effects of an impoverished environment associated with standard housing, effects were assessed using rats housed in a complex enriched environment (EE). Our results show that in comparison to EE alone, middle-aged rats receiving both chronic ampakine treatment and EE were markedly improved in all measures and, in some cases, indistinguishable from young adults. Effects on behavior were particularly striking with ampakine treatment improving long-term memory and self-organizing behavior in an unsupervised learning task. These results suggest that environmental complexity alone is not sufficient to overcome effects of aging on neuronal structure and function but that ampakine treatment can indeed offset structural atrophy and impairments in cognitive function. However, in another study we found that EE rearing alone can promote dendritic branching and increase spine head volume in wild type mice, though these treatment effects were blunted in an intellectual disability mouse model (the Fmr1-KO model of Fragile X syndrome). In fact, EE rearing revealed greater effects of genotype than were evident with standard housing suggesting that it is valuable for animal studies to incorporate exposure to enriched circumstances, more akin to the human experience, to best appreciate the effect of mutations and potential therapeutics on brain function. As will be discussed, a therapeutic approach that combines environmental enrichment with facilitation of BDNF expression, as effected by ampakines, could prove useful for improving learning and memory in both developmental disorders and aging. (Funded by NIH grants P01NS45260 and R01MH082042).

Dysbindin-1 genetics modulate cognitive responses to antipsychotics through D2-related mechanisms within the prefrontal cortex. Diego Scheggia1, Rosa Mastrogiacomo1, Maddalena Mereu2, Sara Sannino1, Richard E. Straub3, Marco Armando4, Francesca Managò1, Fabrizio Piras5, Maria A. De Luca6, Daniel R. Weinberger3, Gianfranco Spalletta5, Francesco Papaleo1. 1Department of Neuroscience and Brain Technologies, Istituto Italiano di Tecnologia, via Morego, 30, 16163 Genova, Italy. 2Dipartimento di Scienze del Farmaco, Universita' degli Studi di Padova, Largo Meneghetti 2, 35131 Padova, Italy. 3Lieber Institute for Brain Development, Johns Hopkins University Medical Campus, Baltimore, Maryland 21205. 4Department of Neuroscience, Bambino Gesù Children's Hospital, Piazza Sant'Onofrio 4, 00100 Rome, Italy. 5IRCCS Santa Lucia Foundation, Neuropsychiatry Laboratory, Rome, Italy. 6Department of Biomedical Sciences, Università di Cagliari, Italy. Schizophrenia is an heterogeneous disorder affecting more than 25 million people worldwide and characterized by a strong genetic component. Antipsychotics are currently the first-line and most largely used medications for the management of schizophrenia spectrum and other psychotic disorders. While these drugs generally ameliorate positive symptoms, clinical responses for negative symptoms and cognitive impairments are non-optimal and highly variable. Notably, cognitive deficits are considered the main source of disability, having the most critical impact on public health and long-term outcomes. Because of the clinical heterogeneity and high therapeutic variability, guidelines strongly recommend adapting antipsychotic treatments to each individual case. However, no biological rationale still exists to implement more effective and personalized healthcare in schizophrenia. Similarly, the mechanisms underlying the unpredictable variability to antipsychotics effects are unknown. Here we found a pharmacogenetics interaction in schizophrenia core cognitive dysfunctions. In particular, results from patients with schizophrenia and genetically modified mice indicated that genetic variations reducing dysbindin-1 conferred better executive control responses to antipsychotics. By lentiviral vector-mediated microRNA silencing manipulations, we demonstrated that in vivo the antipsychotics-by-dysbindin-1 interaction mechanistically relied on dopamine D2 receptors functioning within the medial PFC. Furthermore, we established that this pharmacogenetics effect resides in the functional enhancement of D2 intracellular trafficking in carriers with reduced levels of dysbindin-1 only following the treatment with antipsychotics. These findings highlight a genetic indicator for the implementation of personalized medicine for cognitive disabilities in schizophrenia based on a concrete biological mechanism.

Ras-ERK signalling in Intellectual Disability and Autism Spectrum Disorder: a pathway to the cure? Riccardo Brambilla1. 1Neuroscience and Mental Health Research Institute, Division of Neuroscience, School of Biosciences, Cardiff University, United Kingdom. I will address cellular mechanisms and experimental therapeutic approaches for intellectual disability (ID) associated to neurodevelopmental disorders (NDD), including RASopathies and Autism Spectrum Disorders (ASD). In recent years it has become evident that at the basis of ID and ASD are profound alterations in cell signalling mechanisms in the brain and these alterations occur during early postnatal developmental stages through the interaction of vulnerability genetic factors and environmental processes. A major emphasis will be given to the implications of the Ras-ERK signalling cascade in ASD and in RASopathies, which have extensively been studied in recent years. More specifically the issue of the best therapeutic temporal window will be discussed considering that these disorders are very heterogenous in nature and a careful identification of both genetic and environmental factors is the key toward a precision medicine approach to therapy and possibly to cure.

13:30-15:30 **Symposium: Estrogenic regulation of social behavior.** Chair: Sonoko Ogawa. *Setouchi Hall, Room 1-2*

Estrogen action on neural network of social behavior in mice. Sonoko Ogawa. Laboratory of Behavioral Neuroendocrinology, University of Tsukuba. We have been studying brain mechanisms of social behavior by focusing on the role of two types of estrogen receptors, ERα and ERβ. Previous studies have revealed that they are differentially involved in the regulation of sex-typical expression of social behavior by gonadal steroids such as testosterone (after being aromatized) and estradiol. In a series of studies using adeno-associated viral vector mediated RNA interference methods, we identified brain site(s) and time in development responsible for estrogen action via ERα and ERβ in the expression of sexual, aggressive and parental behaviors (Sano et al., EJN, 2012; Sano et al., PNAS, 2016; Nakata et al., eNeuro, 2016). These studies have revealed that in adult male mice ERα in the ventromedial nucleus of the hypothalamus plays a role in the induction of both sexual and aggressive behavior, whereas in the medial preoptic area it is only involved in sexual behavior. We have also found that although it may not be required at the time of testing, ERα activation in the medial amygdala during pubertal period is crucial for male mice to fully express their male-type social behavior in adulthood. Knockdown of ERβ in the medial amygdala and medial preoptic area hardly affected male sexual and aggressive behavior, except we found that ERβ in the medial amygdala might play a role in the regulation of sexual preference. In females, silencing of ERα and ERβ in these brain areas differently affected the expression of sexual behavior, pup-directed maternal care and postpartum aggression. We not only have found that ERα in the ventromedial nucleus of the hypothalamus is necessary for female sexual behavior but also found that ERβ in the dorsal raphe nuclei may be involved in inhibitory regulation of sexual behavior. In postpartum females, maternal caring behavior was reduced by a lack of ERα in the medial preoptic area, whereas the levels of aggression toward male intruder mice were decreased by ERβ knockdown in the medial amygdala but increased by knockdown in the medial preoptic area. In this talk, we will first overview these findings by focusing on neural network of social behavior. We will then discuss our more recent studies on the effects of manipulation of neuronal activity of ERα expressing neurons with the use of optogenetic and/or pharmacogenetic methods on the expression of sex-typical social behavior. (Supported by KAKENHI #15H05724 to SO)

Sexual differentiation of novel sexually dimorphic nucleus of dorsal hypothalamus in mice. Shinji Tsukahara. Saitama University. Identification of sexually dimorphic nucleus (SDN) is critical to understanding of sex-biased brain functions. Although a number of SDNs have been identified, there remains the potential to uncover novel SDNs. We recently found a novel SDN in the dorsal hypothalamus of mice (hereafter the SDN-DH). The SDN-DH exhibited female-biased sex differences in volume and neuron number and was located between two male-biased SDNs, the calbindin-sexually dimorphic nucleus and the principal nucleus of the bed nucleus of the stria terminalis. Gonadal sex steroids are critical factor for sexual differentiation of the SDN-DH. The volume and neuron number of the SDN-DH were increased in males by neonatal orchidectomy and decreased in females by treatment with testosterone, dihydrotestosterone, or estradiol within 5 days after birth. Sex differences of the SDN-DH emerged before puberty and became prominent in adulthood with increasing volume in females and a loss of neurons in males during the pubertal/adolescent period. Prepubertal orchidectomy did not affect the male SDN-DH, whereas prepubertal ovariectomy disturbed increasing the volume and induced a loss of neurons in the female SDN-DH. Testicular testosterone during the postnatal period may act to defeminize the SDN-DH via binding to androgen receptor and to estrogen receptor after aromatization. Defeminization of the SDN-DH may proceed independently of testicular hormones during the pubertal/adolescent period. Ovarian hormones during the pubertal/adolescent period may act to

feminize the SDN-DH. As one step to clarify the physiological roles of the SDN-DH, we measured neuronal activity with c-Fos, a neuronal activity marker, in the female SDN-DH during maternal and sexual behaviors. The number of c-Fos-expressing neurons was negatively correlated with maternal behavior performance, but it did not change during female sexual behavior. The SDN-DH of female mice may contain a neuronal cell population, the activity of which decreases in females exhibiting higher performance of maternal behavior. Additionally, an area that appears to be homologous with the mouse SDN-DH was found in the dorsal hypothalamus of common marmosets. The sexually dimorphic structure of the dorsal hypothalamus is not specific to mice and may be found in other species.

Rapid actions of estrogens on social behaviour. Vasudevan, Nandini1, Clark, Sara2, Rainville, Jennifer2, Anchan, Divya2. 1: School of Biological Sciences, University of Reading, WhiteKnights Campus, Reading, United Kingdom RG6 6AS. Email: n.vasudevan@reading.ac.uk. 2: Cell and Molecular Biology Department, Tulane University, New Orleans, LA 70125. Steroid hormones are necessary for the display of several social behaviours driven by the hypothalamus, in rodents. We are particularly interested in how estrogens act to drive aggression in male rodents. Steroids such as estrogen and corticosterone regulate transcription slowly by binding to classical, intracellular nuclear receptors but also signal rapidly via membrane receptors that activate kinases and calcium flux. Our previous work also uncovered a third pathway i.e. integrated signaling where rapid non-genomic signaling by 17□-E potentiates transcription via the phosphorylation of the estrogen receptor (ER)□. Using this as a framework, our current studies investigate the contribution of a membrane ER called GPER1 or GPR30 to social behaviours such as lordosis or female sex behaviour where integrated signaling is implicated. Pharmacological activation of GPER1 can increase lordosis in female mice. We will present data here on the regulation of spinogenesis by GPER1 in these females. Estrogen is also critical for the display of both sex and aggressive behaviour in males but since most data is gathered in mice that are treated over long periods of time with estrogen, less is known about the rapid non-genomic signaling that may affect this behaviour. We showed that rapid signaling initiated by the activation of GPR30 can decrease anxiety within 30 minutes in males but not in female mice. We also show that rapid signaling by 17□-E can, within 20 minutes, increase aggression and decrease anxiety in male mice that have been administered letrozole, an aromatase inhibitor. Our data show that ER□ and GPER1 activation are not the main modulators of this behaviour. In addition, letrozole treated male mice show lower basal and stress-induced corticosterone levels that were partially rescued within 20 minutes by estrogen administration. Corticosterone increases aggression rapidly, though the mechanisms remain unknown; our preliminary data suggest that GR activation can rapidly increase aggression. Our data suggest reciprocal interactions between estrogen and corticosterone in male rodents that can rapidly increase aggression. Supported by NSF CAREER IOS-1053716 and partially by Tulane Startup Funds to NV.

Estrogenic regulation of social recognition and social learning in mice. Choleris, Elena; Phan, Anna; Lymer, Jennifer M.; Sheppard, Paul A. S.; Clipperton-Allen, Amy E.; Ervin, Kelsy S.; Gabor, Christopher S.; Paletta, Pietro. Department of Psychology and Neuroscience Program, University of Guelph, Guelph, ON, Canada. Social living requires various cognitive skills including social recognition, the ability to distinguish between conspecifics within a social group. In addition, group living allows for the opportunity to use others as a source of adaptive information. Through social learning animals can acquire multiple skills and information, including which foods are good for consumption. Estrogens affect social cognition via delayed and longer term genomic mechanisms as well as rapid and short lasting non-genomic modes of action. Our findings suggest that social recognition and social learning, while both promoted by estrogens,

are differently regulated by the 3 better known receptors for estrogens: ER□, ER□ and the G protein-coupled estrogen receptor 1 (GPER1). Using ER "knockout" mice we have demonstrated an important role for ER□ and a lesser role for ER□ in social recognition in female mice. Conversely, with the use of ER-specific agonists administered 2-3 days prior to testing we have shown that selective ER□ activation blocked, whereas an ER□ agonist prolonged, a socially acquired food preference, suggesting differing roles for ER□ and ER□ in social recognition and social learning, likely via delayed genomic mechanisms. We also found that the 3 main ERs are differently involved in the regulation of social recognition and social learning via rapid mechanisms and that this involvement is often different from that of the delayed genomic effects. With systemic administration of either 17□-estradiol (E2) or ER-specific agonists we found that within 40 min of treatment E2 or a GPER1 agonist enhanced both social recognition and social learning. However, an ER□ agonist enhanced social recognition and blocked social learning and an ER□ agonist impaired both types of social cognition. With subsequent investigations, we further showed that the dorsal hippocampus plays an important role in estrogens' effects on social recognition but not in social learning. Infusion of either E2, or agonists for ER□ or GPER in the dorsal hippocampus promoted social recognition in ovariectomized female mice, whereas an ER□ agonist was ineffective. Conversely, infusion of E2 in the dorsal hippocampus did not restore social learning in ovariectomized mice. We subsequently showed that the dorsal hippocampus is not the sole mediator of estrogens' enhancing effects on social recognition. Medial amygdalar infusion of E2, as well as the agonists for each of the three ERs restored social recognition in ovariectomized mice. Similarly, infusion of E2 in the paraventricular hypothalamic nucleus promoted social recognition. In summary, our investigations are highlighting a network of brain regions involved in estrogenic regulation of social cognition and are showing differential involvement of the three better known ERs in social recognition and social learning in different regions of the brain. Supported by NSERC.

13:30-15:30 **Symposium: Modeling dimensions of neuropsychiatric disorders.** Chairs: Noboru Hiroi and Francis Lee. *Setouchi Hall, Room 6*

Deconstructing 22q11.2 copy number variants into dimensions of schizophrenia and autism. Noboru Hiroi, PhD. Department of Psychiatry and Behavioral Sciences, Dominick P. Purpura Department of Neuroscience, Department of Genetics, Albert Einstein College of Medicine. Many genetic variants with robust association with neuropsychiatric disorders are now known, and they have been recapitulated in genetic mouse models in an attempt to delve into their mechanistic bases. Because of their exceptional degrees of association, copy number variants (CNVs), a few hundred kilobase to megabase hemizygous deletion and duplication of the human chromosomes, have emerged as promising genetic variants to delve into neuronal and cellular mechanisms underlying neuropsychiatric disorders, and mouse models of CNVs have been--and are being-- developed since 2007. However, the robust association of 22q11.2 CNVs with neuropsychiatric disorders has been known since 1992 and a number of 22q11.2 CNV mouse models have been analyzed in detail. Several issues have emerged from these mouse models of 22q11.2 and other CNVs, including their reproducibility and genuine relevance of behavioral and neuronal phenotypes to human psychiatric disorders. To illustrate pitfalls of these mouse models, I will describe our work that was designed to identify driver genes and cellular substrates for distinct dimensional aspects of schizophrenia and autism associated with 22q11.2 CNVs. I will also illustrate pitfalls of CNV mouse models and strategies to circumvent them. Supported by NIH (R21HD05311, R01MH099660 and U54HD090260), NARSAD, Maltz foundation and Astellas to NH.

Impact of common polymorphisms on the developmental regulation of fear learning and anxiety behavior. Lee, Francis1. 2Department of Psychiatry, Weill Cornell Medical College of Cornell University, New York, New York. The value of common genetic polymorphisms in guiding clinical psychiatry is limited by the complex polygenic architecture of psychiatric disorders. Common polymorphisms have too small an effect on risk for psychiatric disorders as defined by clinical phenomenology to guide clinical practice. To identify polymorphic effects that are large and reliable enough to serve as biomarkers requires detailed analysis of a polymorphism's biology across levels of complexity from molecule to cell to circuit and behavior. In this talk, common human genetic variants in the growth factor, brain-derived neurotrophic factor (BDNF), and in the endocannabinoid system will be highlighted in a series of cross-species studies relating fear learning to anxiety across development. These studies provides examples of how such a vertically integrated translational approach can identify robust genotype-phenotype relationships that have relevance to optimizing psychiatric treatment for the biological states of the developing brain.

Endophenotype in the brain: A key concept for understanding the relationships between genes and behavior. Tsuyoshi Miyakawa. Division of Systems Medical Science, Fujita Health University, Japan. Genetic studies have revealed millions of polymorphisms in human genome, and theoretically, these polymorphisms can have infinite possible combinations. However, it is well-accepted that the human personality can be represented by a small number of traits and that extreme forms of personalities can be categorized into a limited number of psychiatric disorders. An interesting question is: how, despite such huge genomic variability, are there distinct categories of individuals showing similar behavioral patterns? We have been investigating the relationships between genes and behaviors by using a comprehensive behavioral test battery in genetically engineered mice. This test battery covers a broad range of behavioral domains, such as sensorimotor functions, emotionality, and cognition. So far, we have subjected more than 170 different strains of mutant mice to this test battery. Among them, α calcium/calmodulin-dependent protein kinase II heterozygous-knockout (α-CaMKII HKO) mice show several strong behavioral phenotypes, such as hyper-locomotion, abnormalities in social behavior, and a working memory deficit. Detailed molecular and electrophysiological analyses revealed that almost all neurons in their dentate gyrus are in a pseudo-immature status; we named this phenotype "immature dentate gyrus (iDG)." Surprisingly, this phenotype is observed in several other strains of mutant mice showing behavioral phenotypes similar to that of α-CaMKII HKO mice as well as in wild-type mice subjected to chronic anti-depressant treatment or having epileptic seizures. Moreover, molecular expression analyses of post-mortem brains suggest that the iDG phenotype exists in certain populations of patients with psychiatric disorders, such as schizophrenia and bipolar disorder. The iDG phenotype might be an intermediate phenotype or an endophenotype onto which many unique genetic and non-genetic features converge and through which a similar pattern of behavioral traits emerges. By using iDG as an example, I will discuss the impact of "endophenotype of the brain" concept on understanding the pathways linking genes to behavior and on investigations into the pathogenesis and pathophysiology of neuropsychiatric disorders.

Unraveling the dimension of 16p11.2 copy number variant syndromes, a comparative studies using rodent models. Yann Herault1,2,3,4,5, Valérie Nalesso1,2,3,4, Sandra Martin Lorenzo1,2,3,4, and Thomas Arbogast1,2,3,4*. 1. Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Université de Strasbourg, Illkirch, France. 2. Centre National de la Recherche Scientifique, UMR7104, Illkirch, France. 3. Institut National de la Santé et de la Recherche Médicale, U964, Illkirch, France. 4. Université de Strasbourg, Strasbourg, France. 5. CELPHEDIA, PHENOMIN, Institut Clinique de la Souris (ICS), 1 rue

Laurent Fries, F-67404 Illkirch-Graffenstaden, France. *present address : Center for Human Disease Modeling, Duke University, 300 N. Duke Street, Durham, NC 27701, USA. The 16p11.2 deletion and duplication syndromes are part of those CNV syndromes with rearrangement affecting a 600Kb conserved region with 29 genes. The population prevalence has been defined of approximately 1/2000 based on severe clinical outcomes. Symptoms indicate that 16p11.2 CNVs induce opposite effects on morphology, metabolism and brain function with the deletion associated with autism spectrum disorder (ASD), whereas the duplication has been associated to autism as well as schizophrenia. To identify dosage-sensitive gene(s) which expression changes lead to the antagonistic CNV phenotypes, we generated new mouse models for the deletion and duplication of the 16p11.2 homologous region, in the mouse that we characterized with an exhaustive series of behavioral and metabolic tests. We explored the contribution of two different genetic contexts and additional parameters and we pursued the analysis with single candidate knock-out. Overall the 16p11 region genetic dosage induced similar consequence in mice and humans with activity and memory alterations, but we found that the metabolic defects were opposite in the two species. Together, these data indicate that the dosage imbalance at the 16p11.2 locus perturbs the expression of modifiers outside the CNV that can modulate the penetrance, expressivity and direction of effects in both humans and mice. Now we are investigating new rodent models in particular for candidate genes in the mouse in order to identify the major genetic driver if any exist for the 16p11.2 CNV syndromes. Funding acknowlegdment: European Union (FP7 Gencodys, grant 241995), Grants from the “Agence Nationale de la Recherche” (ANR-15-CE16-0015-01) and French Government for the Investments for the Future the IDEX02 and labex INRT (ANR-10-IDEX-0002-02 ; ANR-10-LABX-0030-INRT) and the National Infrastructure for Biology and health PHENOMIN (ANR-10-INBS-07) and “Fondation Maladies Rares” to YH.

16:00-18:00 **Symposium: Synthetic psychoactive cathinones (i.e., “bath salts”): Separating fact from fiction.** Chair: Frank Hall. *Setouchi Hall, Room 6*

Assessment of the Aversive and Rewarding Effects of Synthetic Cathinones: Implications for Drug Use and Abuse. Anthony L. Riley, Katharine Nelson and Claudia J. Woloshchuk. Center for Behavioral Neuroscience, American University, Washington DC 20016 Drugs of abuse have historically been examined in animal models, given the obvious limitations on such experimentation in humans. The preclinical model with the most face validity for human drug taking is drug self-administration in which animals are allowed to respond for the delivery of a specific drug and the rate and level of responding indicates the overall affective response to that drug. Such a procedure has been widely used since its initial demonstration, and a wide range of compounds used and abused by humans support self-administration. Although self-administration is well established in preclinical work, drug taking in animals (and humans) is thought to reflect the balance of the drug’s rewarding and aversive effects and understanding and predicting abuse vulnerability necessitates an awareness of each property and the multiple factors that may influence them and their balance. In this context, the behavioral assessment of the use and abuse of synthetic cathinones becomes critical. Synthetic cathinones are the active component in most products known colloquially as “bath salts”. These drugs initially appeared in reports from the CDC and emergency rooms across the United States in 2010, and at the outset these products could easily be purchased over the internet or in small retail locations such as head shops and gas stations. Often causing severe hallucinations, paranoia, violent behaviors, tachycardia and even death, they pose a significant threat, and yet they are relatively unknown compared to other abused compounds. It is clear from clinical assessments and reports in human populations that the synthetic cathinones possess some

level of abuse potential. A recent investigation by Johnson and Johnson (2014) surveyed 113 individuals using these compounds and noted that over 50% of the respondents met DSM-V criteria for substance use disorder. These compounds act primarily on the monoaminergic reward systems in the brain and in a manner similar to other stimulants known to pose a risk for abuse and dependence. That these drugs are self-administered by humans and act on neurotransmitter substrates associated with reward, i.e., the monoamines and, particularly, dopamine, suggests that they have some measure of abuse potential. In order to more thoroughly assess this potential, particularly given the wide variety of these compounds presently on the illegal drug market, it is important to return to preclinical animal models. In this presentation, we will discuss the available data concerning synthetic cathinone selfadministration, the rewarding and aversive effects of these compounds (as assessed in a variety of preclinical assays), factors that influence their subjective effects and how these factors may contribute to predicting their overall intake and abuse liability.

Preclinical evaluation of the addictive potential of new synthetic cathinones. Peng Xu 1, Dan Wang 1, Youmei Wang 1, Hao-wei Shen 2. 1. Drug Intelligence and Forensic Center, Ministry of Public Security, Beijing, PR China. 2. Ningbo University School of Medicine, Zhejiang Province, PR China. Synthetic cathinones have become increasingly popular as new psychoactive substances in China and other countries. Due to the diversity of their structural and pharmacological characteristics, little data exist on the behavioral properties produced by the second generation of synthetic cathinones. Here we reported the effects of several synthetic cathinones (methcathinone, flephedrone, 4-methylethcathinone, ethylon, 4-Fluoromethamphetamine and α-PVP) which were found in smuggling or trading on the black market on reward-associated behaviors. Our results demonstrated that conditioned place preference (CPP) could be included by all these synthetic cathinones. Repeated methcathinone, but neither flephedrone nor 4-methylethcathinone produced locomotor sensitization. 4-Fluoromethamphetamine and α-PVP resulted in consistent intravenous self-administration and discrimination for the drug-paired lever, while ethylon caused low and inconstant drug intake. These results suggest that synthetic cathinones produced variable behavioral properties, and their addictive potential need to be judged by integrating multiple types of reward-associated behavioral experiments.

Synthetic psychoactive cathinones and neurotoxic amphetamines: Critical structural elements that determine neurotoxicity. Kuhn, Donald M.1,2, Angoa-Perez, Mariana1,2 and Anneken, John H1,2. 1Research & Development Service, John D. Dingell VA Medical Center and 2Department of Psychiatry & Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, Michigan, USA. The synthetic psychoactive cathinones (SPC) such as methcathinone (MeCa), mephedrone (Meph) and 3,4-methylenedioxypyrovalerone (MDPV) are drugs that have significant abuse potential. These drugs are also components of what have been referred to in the popular press as “bath salts”. Despite being touted initially as legal and safe substances, these compounds are now illegal and highly regulated, and their effects can be extremely dangerous and even lethal. The SPCs bear a remarkable similarity in chemical structure to the amphetamine psychostimulants. Some members in this drug class are known to exert highly toxic effects on the CNS and include methamphetamine (Meth) and 3,4-methylenedioxy-methamphetamine (MDMA, Ecstasy). Based on the similarities in the behavioral and neurochemical properties of the SPCs and the neurotoxic amphetamines, we hypothesized that the SPCs would cause damage to dopamine (DA) nerve endings like that observed after Meth intoxication. Our initial studies comparing Meph to Meth were very surprising and showed that Meph was not neurotoxic, despite administration of high doses of the drug to mice using a well-characterized binge protocol. Subsequent

experiments revealed that non-neurotoxic doses of Meph significantly enhanced the neurotoxicity of Meth. Two structural modifications of Meth- addition of a 4-methyl group and a β-keto- results in Meph. Thus, we tested the intermediates between Meph and Meth- namely MeCa and 4-methyl-Meth (4MM)- for their neurochemical effects. MeCa shows neurotoxic effects that are intermediate to those of Meth while 4MM is non-neurotoxic like Meph. Combined treatment with SPCs and the amphetamines reveals a complex set of interactions that can result in heightened neurotoxicity or neuroprotection. Ongoing studies are revealing that the 4-methyl group and the β-keto moiety determine the relative efficacy of drugs bearing these structural components in interacting with presynaptic storage vesicles. The 4-methyl group is non-reactive with the vesicle monoamine transporter (VMAT) and is non-neurotoxic while the β-keto-amphetamines and selected amphetamines react potently with the VMAT and result in damage to at least DA nerve endings. Supported by a CEBRA grant from the National Institute on Drug Abuse.

Lethal and toxic effects of synthetic psychoactive cathinones. F. Scott Hall, Dawn Muskiewicz, Yasir Saber, and Federico Resendiz-Gutierrez. Dept. Pharmacol. & Exp. Therapeutics, Coll. Pharm. & Pharm. Sci., Univ. of Toledo, OH, USA. Background. Synthetic psychoactive cathinones (SPCs) have similar psychostimulant and entactogenic properties to methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA). SPC abuse has been with adverse events, emergency room admissions, and lethal overdoses, and it has been suggested that these risks are greater than for METH or MDMA. In an initial study we found that the LD50 for the SPC methylone was slightly lower than METH or MDMA. Here we report findings for a number of other SPCs. Methods. LD50 studies were performed for the SPCs cathinone, methcathinone, methylenedioxypyrovalerone (MDPV), and mephedrone, as well as MDMA and METH, in adult male and female C57BL/6J mice. Subjects were injected with 0-120 mg/kg (base) IP of a test drug; 6 doses were tested for each drug, temperature was measured at 20 min intervals for 2 hr, and behavioral observations made (e.g. hyperlocomotion, seizure, 5-HT behavioral syndrome, etc.). Results. LD50 values for METH and MDMA were 84.1 and 92.2 mg/kg respectively. Low doses produced locomotor activity replaced by stereotypy at higher doses. Slight hyperthermia was observed at some doses. At high doses convulsions and death occurred within minutes. The LD50 for mephedrone was 105.4 mg/kg; convulsions and death similarly occurred within minutes at the highest dose. By contrast, neither lethality nor convulsions were observed for MDPV, cathinone, or methcathinone. Moreover, pronounced dose-dependent hypothermia was observed – as much as 7-8 °C. Conclusions. The SPCs studied here (MDPV, mephedrone, cathinone or methcathinone) had LD50 values higher than METH and MDMA. The highest dose of mephedrone induced lethality and convulsions at the highest dose, but reduced body temperature. Even more pronounced hypothermia was observed with cathinone, methcathinone and MDPV, but was not associated with lethality. These data indicate that: (1) not all SPCs exhibit greater lethality than METH and MDMA (at least under the conditions studied here); (2) SPCs differ substantially in their effects on thermoregulation; (3) as we have previously found for methylone, effects of SPCs on temperature appear to be independent of effects on lethality.

16:00-18:00 **Symposium: Insulin and glucose: What's new in metabolic regulation of memory?**
Chair: Ewan McNay. *Setouchi Hall, Room 1-2*

Insulin and beta-amyloid: opposing modulators of hippocampal cognitive and metabolic processes. McNay, Ewan C.[1], Pearson-Leary, Jiah, Osborne, Danielle M.[1 1.] Behavioral Neuroscience, University at Albany. Over the past decade, it has become increasingly recognised that type 2 diabetes (T2DM) is a major risk factor for development of subsequent dementia, and specifically of Alzheimer's disease (AD). Several large epidemiological studies have confirmed that T2DM may be the single largest cause of AD.

This link is increasingly supported by molecular evidence: the brains of Alzheimer's patients show impaired insulin signalling, and studies primarily in neuronal culture systems have shown that insulin and beta-amyloid (Aβ) - the proteins whose over-accumulation defines T2DM and AD respectively - interact directly. For example, increased insulin prevents breakdown of Aβ, which then feeds back to block insulin receptors in what is likely to be a vicious spiral towards dysfunction and AD. We previously showed *in vivo* that Aβ directly impairs hippocampal signalling and metabolism; we also showed that (i) delivery of insulin directly to the hippocampus acutely increases hippocampal metabolic and cognitive processes, and (ii) that inhibition of endogenous hippocampal insulin produces profound memory deficits, showing that insulin is a critical component of hippocampal cognitive physiology. Here we discuss recent work that identifies the insulin-regulated glucose transporter GluT4 as having a central role in these effects. Secondly, we discuss recent work from the lab showing that intrahippocampal blockade of oligomeric Aβ can reverse cognitive and neurochemical impairments seen in a rat model of T2DM, suggesting that abnormal accumulation of Aβ is a critical, causal step in diabetic cognitive decline even well before dementia occurs. This set of findings suggest that not only is T2DM a major risk factor for cognitive decline and development of AD, but that in fact the cognitive and neural impairments seen in patients with T2DM may be due, at least in part, to a pre-AD state characterised by abnormal elevation of oligomeric beta-amyloid in the brain.

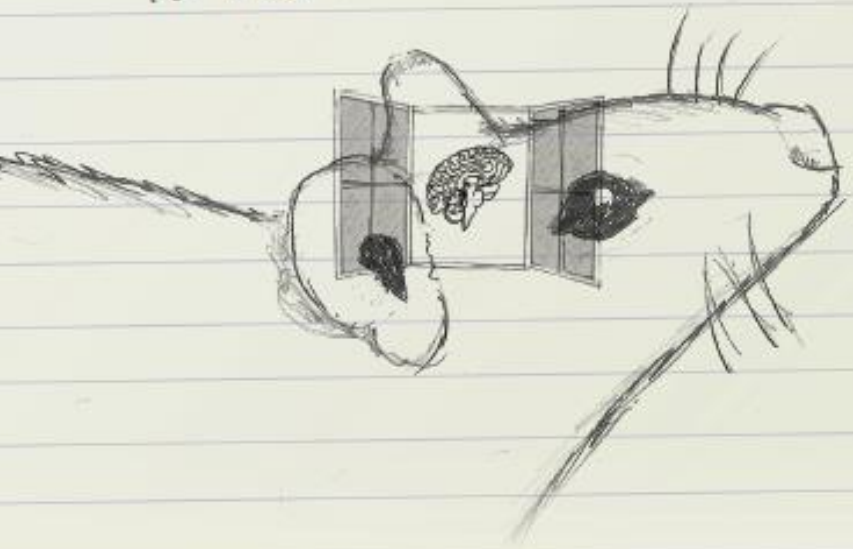
Impaired memory and hippocampal function on a high-fat diet: Sex-differences in hormonal regulation, metabolism, neuronal excitability, and insulin-sensitivity. Thompson, Lucien T.[1]; Tandon, Neha R.[1]; Underwood, Erica L. [1,2]. [1]Neuroscience, BBS, University of Texas at Dallas; [2]Pediatric Nutrition, Baylor College of Medicine. Excess ingestion of energy-dense fats promote obesity, metabolic syndrome and insulin-resistant type-2 diabetes, a public health crisis impacting society worldwide. In rat models, feeding a high-fat diet (HFD) from weaning severely impairs hippocampal function and memory consolidation, similar to impairments of humans suffering from diabetes or obesity. Sex differences are rarely systematically assessed or compared. Littermate male and female LE rats were fed from weaning control or HFD (57.6% fat, 26.8% carbohydrate, 15.6% protein) for 12 wk. Spatial memory was assessed in spatial objection recognition and spontaneous alternation tasks; plasma collected for ELISAs; and estrus assessed by vaginal cytology. Protein expression was assessed from lysates of flash frozen brain punches via western blots, or perfused brains via IHC/IFC. Fresh brain slices were also rapidly prepared for *in vitro* recordings from CA1 pyramidal neurons to assess post-burst AHPs, accommodation, etc., then sensitivity to bath application of 12.5 nM insulin was tested. Both sexes consuming HFD exhibited significantly impaired spatial memory compared to controls. HFD males developed clinically-relevant symptoms of type-2 diabetes (obesity, loss of blood glucose control, elevated circulating insulin), but HFD females did not (normal weight and blood glucose control, reduced circulating insulin, with no changes in estrogen nor estrus cycling). Multiple other dietary-signaling pathways as well as those regulating neuronal excitability exhibited sex-dependent changes. CA1 neurons from both males and females exhibited significantly reduced intrinsic excitability, with corresponding upregulation of SK channel expression. However, CA1 neurons in females but NOT in males remained insulin-sensitive, with insulin receptor expression maintained. While both males and females exhibited significant deficits on both memory tasks, cognitive deficits in males—those presenting with diabetic symptoms—would more likely be assessed and treated. Covert female deficits (no clinical symptoms) would likely remain undiagnosed. Given profoundly different biological responses shown by females to HFD, follow-up treatments effective in males are unlikely to be productive in females. These novel findings indicate critical public health issues for assessing and treating females and males differently. Support from Clark Foundation, ATA, Project Emmett, & BBS.

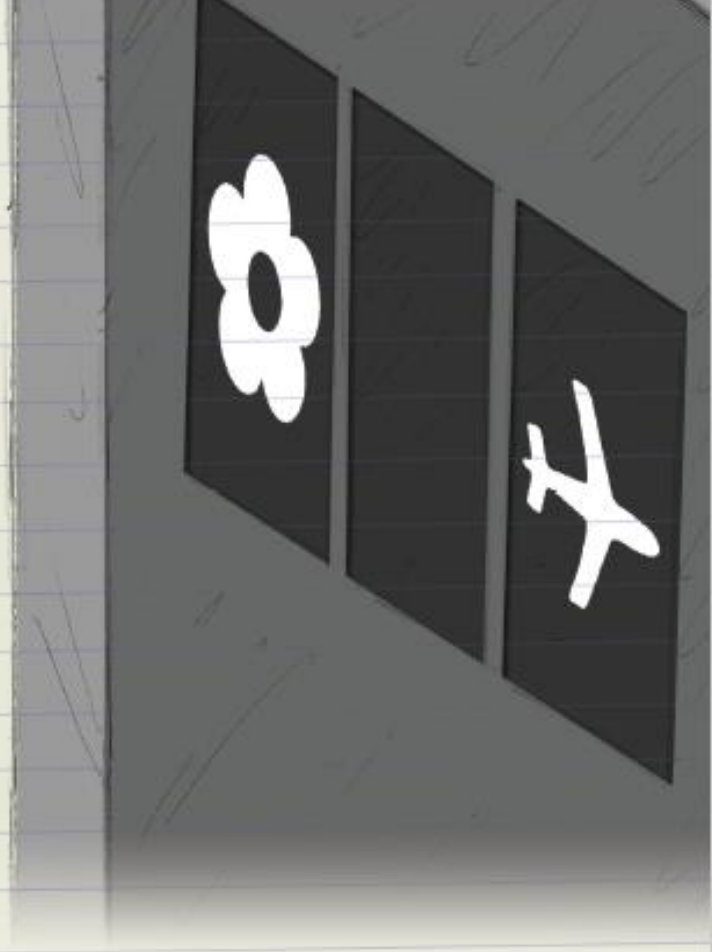
Maintaining insulin signaling to offset cognitive decline with aging. Olivier Thibault, University of Kentucky, Department of Pharmacology and Nutritional Sciences, UKMC MS-313, Lexington, KY 40536.Our lab has been studying the neuroscience of learning and memory in young and aged animals and elucidating mechanisms underlying cognitive aging. Our more recent focus has been on how key peripheral hormones influence neuronal excitability and memory processing. The overall goal of our studies is to develop interventions which promote healthy brain aging and ultimately improve neurological outcomes in diabetes by identifying strategies (novel ligands/treatments) that may counteract cognitive decline in aging and Alzheimer's disease. Therefore, we have been specifically testing whether identified mechanisms of cognitive aging are sensitive to insulin by characterizing memory recall and associated signaling pathways in animals treated with intranasal insulin. Here, we present evidence that different insulin preparations have d¬ifferent behavioral outcomes in young and aged animals. Using electrophysiological techniques, we also show that acute insulin exposure can reduce a calcium-dependent hyperpolarizing potential in hippocampal pyramidal neurons. A combination of calcium imaging and patch clamping techniques also reveal that increased insulin signaling acutely reduces voltage-gated calcium currents and calcium levels in hippocampal neurons in culture and, thus, may represent the underlying mechanism for the reduced hyperpolarizing potential. Ongoing studies are using two approaches to facilitate insulin signaling: one involves the delivery of a constitutively active truncated beta subunit of the insulin receptor and the other long-term intranasal exposure to Insulin Aspart/Novolog®. Collectively, our evidence supports a novel mechanism for insulin's neuroprotective actions by targeting voltage-gated calcium channels and intracellular calcium sources to reduce the calcium dysregulation characteristic of brain aging (and Alzheimer's). Because the aging population is projected to dramatically increase worldwide, implementing strategies that maintain healthy cognitive function will tremendously benefit this population, and by extension, reduce the incidence of age-related neurodegenerative diseases. Further, as ongoing clinical trials are testing insulin for age-related cognitive decline, our studies also suggest that not all insulin preparations have comparable efficacy. Funding acknowledgements: 5R01AG033649-07.

Glucocorticoid regulation of tau pathology in obesity and diabetes. Aditi Dey,1 Shuai Hao,1 Marlena Wosiski-Kuhn,1 and Alexis M. Stranahan1. 1Department of Neuroscience and Regenerative Medicine, Augusta University, Augusta, GA, USA. Type 2 diabetes is increasingly recognized as a risk factor for Alzheimer's disease (AD), but the underlying mechanisms remain poorly understood. Hyperphosphorylation of the microtubule-associated protein tau has been reported in rodent models of diabetes, including db/db mice, which exhibit insulin resistance and chronically elevated glucocorticoids due to leptin receptor insufficiency. Rodents with diet-induced insulin resistance also exhibit hippocampal tau pathology, but consensus has yet to emerge with respect to changes in glucocorticoids in dietary models. My lab has begun to investigate endocrine mechanisms for hippocampal tau phosphorylation in db/db mice and mice with high-fat diet-induced insulin resistance. By separately manipulating peripheral and intrahippocampal corticosterone levels, we determined that hippocampal corticosteroid exposure promotes tau phosphorylation and activates glycogen synthase kinase 3β (GSK3β), a prominent tau kinase. Subsequent experiments in hippocampal slice preparations revealed evidence for a nongenomic interaction between glucocorticoids and GSK3β. To examine whether GSK3β activation mediates tau phosphorylation and impairs memory in diabetes, db/db and Wt mice received intrahippocampal infusions of TDZD-8, a non-ATP competitive thiadiazolidinone inhibitor of GSK3β. Intrahippocampal TDZD-8 blocked tau hyperphosphorylation and normalized hippocampus-dependent memory in db/db mice,

suggesting that pathological synergy between diabetes and AD may involve glucocorticoid-mediated activation of GSK3β.

ANIMAL BEHAVIOR:
THE WINDOW
TO HUMAN BEHAVIOR





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