IBNS
International Behavioral Neuroscience Society

Annual Meeting Program and Abstracts

Budapest, Hungary
June 7-11, 2016

Abstracts of the 25th Annual Meeting of the International Behavioral Neuroscience Society

Volume 25, June 2016

Contents

IBNS CENTRAL OFFICE

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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 25th Annual Meeting of the International Behavioral Neuroscience Society that is taking place in one of the most beautiful European cities, Budapest, Hungary. IBNS is a unique organization that includes researchers from all over the world with interest in Behavioral Neuroscience. Our meeting, the crown jewel of the Society, is not only another excellent occasion to promote behavioral neuroscience but is also the important milestone in the history of our society as we are celebrating its silver anniversary.

Thanks to the Program Committee and the committee chair, Kim Gerecke, and her co-chair, Anthony Kline, the scientific program of the meeting includes both a remarkable collection of high quality research and an impressive international representation of members and attendees. As we had received many more symposium proposals than we could realistically accommodate in our standard 4-day program, selecting the best proposals was not an easy task but the members of the committee did a superb job and I hope you will find the science of the meeting interesting and inspiring. I would also like to thank the Education and Training committee. They worked hard to choose the most promising young scientists for travel awards, which enabled the awardees to attend the meeting, in order to share their scientific discoveries with us.

We are always grateful to our sponsors for their steady support of the meeting and society. Please, make sure to stop by their stands during meeting breaks to learn latest technological and informational innovations for behavioral neuroscience.

We are proud that our meetings take place in different corners of the world. As an international society, we will continue to bring in new members and promote behavioral neuroscience in countries with rich and developing scientific history alike. Thanks to our Executive Coordinator, Marianne Van Wagner and Business & Event Manager, Alison Watson, this year, we are getting together at the Kempinski Hotel in Budapest. This exciting venue provides excellent meeting space, opportunities for discussions and places to have fun with friends and families. Please, try to find time for sightseeing and learning the rich history of the city.

On a personal note, I am honored and thrilled to lead the society during this special time. Still, only together will we be able to continue to promote behavioral neuroscience throughout the world and ensure that our society will succeed in marching to the future 50th anniversary…and counting.

I am looking forward to a terrific meeting in the heart of Europe.

Best wishes,

Mikhail (Misha) Pletnikov
President IBNS

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USA ..... Jared Young

AWARDS

Career Achievement Award

The 2016 Career Achievement Award will be presented to Stephen Kent, IBNS Past-President, Fellow, for his outstanding professional achievement in the field of Behavioral Neuroscience. He earned his Ph.D. at the University of Illinois at Urbana-Champaign and currently holds the position of Head, School of Psychological and Public Health, La Trobe University, Melbourne, Australia. Dr Kent's early work characterised and helped define the concept of "sickness behaviour", which has helped guide research in psychoneuroimmunology for 20 years. He has published extensively on the behavioural effects of cytokines, the pathways by which the immune system communicates with the CNS, stress resiliency and vulnerability, as well as links between cardiovascular health and depression. For the past 10 years his laboratory has documented how caloric restriction during adulthood and in the perinatal period alters behaviour, physiology and perhaps most intriguingly attenuates inflammatory processes (e.g., fever and sickness behaviour) including reducing neuroinflammation in the hypothalamus. He has been well funded by the Australian Research Council, has given more than 35 invited talks including several keynotes at international conferences, and is on the editorial board for several journals. Dr Kent is Deputy Chair of HODSPA (Heads of Departments and Schools of Psychology Association). He has served IBNS as Australasian Councilor, Program Chairperson, and President along with serving and chairing numerous committees. He will be awarded a plaque during the IBNS Awards Banquet.

Read more about his research interests and career
here: http://www.latrobe.edu.au/psy/about/staff/profile?uname=SPKent

Early Career Achievement Award

The 2016 Early Career Achievement Award goes to Michael Bowen. Michael will receive $500, a waiver for registration fees and will give a talk entitled "Oxytocin inhibits ethanol consumption and intoxication in rats: Interactions with dopamine and extrasynaptic GABAA receptors" on Saturday, June 11, 6:00 p.m. Dr. Bowen's research has led to clinical trials, patents, commercial partnerships, many highly-cited papers in top scientific journals, over $1M in competitive research funding, a prestigious National Health and Medical Research Council Peter Doherty Biomedical Research Fellowship, numerous high-profile national and international research awards, more than 20 invited talks at national and international conferences and public forums, and worldwide media coverage. His status as one of Australia's top young scientists was recently recognized at the 2015 NSW Premier's Prizes for Science and Engineering where he was named Early Career Researcher of the Year. Earlier in 2016, Dr Bowen was invited into the World Economic Forum's Young Scientist community in recognition of his "track recording of advancing the frontiers of science in areas of high society impact".

TRAVEL AWARDS

We are pleased to announce the recipients of the IBNS Travel Awards for the 2016 meeting in Budapest, Hungary. 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 and the IBNS members.

Sarah	Baracz*	University of Sydney	Australia
Laszlo	Biro	Inst. of Experimental Medicine	Hungary
Zsuzsa	Buchwald	Mouse Imaging Center (Sickkids Hospital)	Canada
Robert	Cole	Temple University	USA
Zackary	Cope	University of California San Diego	USA
Matthew	Davenport	Cincinnati Children's Hospital Medical Center	USA
Patricia	de la Tremblaye	University of Pittsburgh	USA
Gabor	Egervari	Icahn School of Medicine at Mount Sinai	USA
Amanda	Facciol	University of Toronto Mississauga	Canada
Theresa	Kisko	Phillips University Marburg	Germany
Steven	Nieto	University of Houston	USA
Richard	O'Connor*	Icahn School of Medicine at Mount Sinai	USA
Timothy	Schoenfeld	National Institute of Mental Health	USA
Dominik	Seffer	Philipps-University Marburg	Germany
Soaleha	Shams	University of Toronto	Canada
Alexandra	Stolyarova	University of California, Los Angeles	USA
Ayse	Sungur	Philipps-University Marburg	Germany
Steven	Tran	University of Toronto	Canada

*These travel awards are sponsored by *Pharmacology, Biochemistry and Behavior* (Elsevier).

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The IBNS would like to express our gratitude to the following organizations that have given financial support to the 25th International Behavioral Neuroscience Society Conference.

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ViewPoint

Please take time to visit the exhibit tables and thank these companies for their support. View more exhibitor information at the end of this program.

ACKNOWLEDGMENTS

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

Program Committee

Kim Gerecke, Chair
Anthony Kline, Co-chair
Mikhail Pletnikov (Council Liaison)
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Robert Gerlai, IBNS Fellow and Past-President, University of Toronto Mississauga, Canada

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

FLOOR PLANS

Kempenski Restaurants

Kempenski Meeting Space

Europa Riverboat Tour Location

PROGRAM

REGISTRATION: Please pick up your name badge on Tuesday, June 7, from 6-7 p.m., before the riverboat tour at the main lobby hospitality desk. 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 and closing reception – no exceptions. There will be a $10 fee for replacement badges. The desk will also be open in Regina 3 for late arrivals.

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

Tuesday, June 7

9:00-1:00 Council Meeting (council members only) *Corvinus Salon*

1:00-6:00 Budapest City Tour (prior reservation required) *Meet in Main Lobby at 12:45 p.m.*

7:00-8:00 Student & Postdoctoral Social / Europa Riverboat Tour *Meet in Main Lobby at 7:00 p.m.*

7:00-10:00 Welcome Reception / Europa Riverboat Tour *Meet in Main Lobby at 7:00 p.m.*

Wednesday, June 8

8:00-10:00 ***Sex differences in the brain: Implications for behavioral and biomedical research.*** Chair: Elena Choleris. *Regina Ballroom 2*

- 8:00 Sex differences in rodent social behavior: Hormonal influences. Choleris, Elena; Clipperton-Allen, Amy; Ervin, Kelsy SJ; Lymer, Jennifer M; Gabor, Christopher S; Sheppard, Paul; Phan, Anna.
- 8:30 Sex matters: Hippocampal neurogenesis, Spatial Learning and Pattern Separation. Galea, Liisa A. M.
- 9:00 Estrogenic regulation of memory in males and females: Molecular mechanisms and implications for aging. Frick, Karyn M.
- 9:30 Sex differences in stroke and stroke therapies. Sohrabji, Farida.

8:00-10:00 ***Epigenetic Regulation of Motivated Behaviors.*** Chair: Zuoxin Wang; Co-Chair: Mohamed Kabbaj. *Regina Ballroom 1*

- 8:00 Role of DNA methyl-cytosine oxidation in cocaine action. Feng, Jian.
- 8:30 Methamphetamine-associated memory is regulated by histone methylation. Miller, Courtney A.

9:00 Influence of genomic imprinting on metabolism and behavior. Lu, Xin-Yun.

9:30 Epigenetics of Social Bonding in Prairie Voles. Kabbaj, Mohamed; Wang, Zuoxin; Liu, Yan; Elvir, Lindsay.

10:00-10:30 **Exhibits – Refreshment Break.** *Regina Ballroom 3*

10:30-11:30 **Keynote: Yasmin Hurd, PhD.**, Mount Sinai Hospital. High Times for Cannabis: Epigenetic Imprint and its Legacy on Brain and Behavior. *Regina Ballroom 1/2*

11:30-1:30 **Lunch.** *Salons*

1:30-3:30 ***Zebrafish and human brain disorders: A new tool in behavioral neuroscience.*** Chair: Robert Gerlai. *Regina Ballroom 2*

1:00 Behavioral, anatomical, and pharmacological phenotyping of zebrafish models of autism. Ellen J. Hoffman, Marcus Ghosh, Katherine J. Turner, Steve W. Wilson, Matthew W. State, Antonio J. Giraldez, Jason Rihel.

2:00 Screening of natural products using zebrafish behavior. Ortiz, Jose G., del Valle-Mojica, L., Rosa-Falero, Coral and Torres-Hernandez, Bianca.

2:30 What makes us social? Analysis of a zebrafish model. Shams, Soaleha.

3:00 Zebrafish and alcohol: A simple vertebrate for a complex disease problem. Robert Gerlai.

1:30-3:30 ***Early life stress and serotonin: Effects on social and emotional health.*** Chair: Jodi Pawluski. *Regina Ballroom 1*

1:30 Prenatal exposure to SSRI antidepressants and lessons we can learn about child development. Oberlander, Tim.

2:00 Effects of differential maternal care on sibling differences in anxiety, mothering, and serotonin mechanisms in rats. Ragan, Christina.

2:30 Developmental epigenetic programming in serotonin-transporter deficient mice. Van den Hove, Daniel.

3:00 Consequences of venlafaxine treatment and/or maternal adversity on neurobehavioral development of rat offspring. Császár Eszter, Melicherčíková Kristína, Mach Mojmír, Ujházy Eduard, Dubovický Michal.

3:00-3:30 **Exhibits – Refreshment Break.** *Regina Ballroom 3*

4:00-6:00 **Travel Award Blitz.** Chairs: Stacey Rizzo and Markus Wöhr. *Regina Ballroom 2*

4:10 A novel oxytocin-like compound reduces motivation to self-administer methamphetamine and relapse to methamphetamine seeking in rats. Baracz, Sarah; Everett, Nicholas; Bowen, Michael; Kassiou, Michael; Cornish, Jennifer; McGregor, Iain.

4:16 The subunit-specific role of NMDA receptors in behavioral dysfunctions evoked by traumatic event. Laszlo, Biro; Eva, Mikics; Eszter, Sipos; Christina, Miskolczi; Mate, Toth; Jozsef, Haller.

4:22 Examining the effect of chronic intranasal oxytocin administration on the neuroanatomy and behaviour in two different autism-related mouse models. Buchwald, Zsuzsa; Stuive, Monique; Ellegood, Jacob; Anagnostou, Evdokia; Lerch, Jason.

4:28 Temporal dissociation of activity-dependent alterations in prefrontal BDNF expression during decision-making shifts. Cole, Robert D.; Parikh, Vinay.

4:34 A gene x environment mouse model of switching between affective states: Reducing DAT function results in hypersensitivity to seasonal photoperiod-induced changes in affect. Cope, Zackary A; Dulcis, Davide; Young, Jared W.

4:40 Loss of neuronal activity in the central amygdala of seizure prone Fmr1 KO mice is conserved across multiple mouse lines susceptible to audiogenic seizures. Davenport, Matthew; Robinson, Chandler; Grainger, Lindsey; King, Andrew; Erickson, Craig; Schaefer, Tori.

4:46 CRHR1 Mediation of neuroplasticity and neuroinflammation in the hippocampus following global cerebral ischemia. Patricia B. de la Tremblaye and Hélène Plamondon.

4:52 Prodynorphin genetic polymorphisms and ventral striatonigral pathway activity contribute to individual differences in novelty seeking and positive reward traits. Egervari, Gabor; Jutras-Aswad, Didier; Landry, Joseph; Miller, Michael; Anderson, Sarah Ann; Michaelides, Michael; Jacobs, Michelle; Peter, Cyril; Yiannoulos, Georgia; Liu, Xun; Hurd, Yasmin L.

4:58 CB1 receptor antagonism increases anxiety-like behavioural responses and alters neurochemical levels in two distinct populations of zebrafish. Facciol, Amanda; Tran, Steven; Chatterjee, Diptendu; Gerlai, Robert.

5:04 SERT on speed: Enhanced emission of amphetamine-induced 50-kHz ultrasonic vocalizations in rats lacking the serotonin transporter due to long-term adaptations in 5-HT2C receptor functioning. Kisko TM, Willadsen M, Vörckel KJ, Seffer D, Schwarting RKW, Homberg J, Wöhr M.

5:10 Sex differences in the effects of naltrexone on appetitive and consummatory responses to ethanol in adult rats. Nieto, Steven J; Winoske, Kevin J; Kosten, Therese A.

5:16 Role for hypothalamic projections to habenula in obesity. Richard M. O'Connor and Paul J. Kenny.

5:22 The impact of neurogenesis on flexible maze training: Effects on hippocampal volume and cognition. Schoenfeld, Timothy; Rhee, Diane; Cameron, Heather.

5:28 Post-weaning social isolation results in ultrasonic communication deficits, cognitive impairments and alterations in microRNA-dependent Ube3a1 function on neuronal plasticity in rodents: Implications for autism. Seffer, Dominik; Rippberger, Henrike; Valluy, Jeremy; Bicker, Silvia; Aksoy-Aksel, Ayla; Lackinger, Martin; Sumer, Simon; Fiore, Roberto; Wüst, Tatjana; Metge, Franziska; Dieterich, Christoph; Schratt, Gerhard; Schwarting, Rainer K.W.; Wöhr, Markus.

5:34 Developmental social isolation alters expression of neural proteins in adult zebrafish. Shams, Soaleha; Chatterjee, Diptendu; Gerlai, Robert.

5:40 Dissociable roles for basolateral amygdala and orbitofrontal cortex in optimal choice behavior under conditions of reward variability. Alexandra Stolyarova, Alicia Izquierdo.

5:46 Aberrant Cognitive Phenotypes and Altered Hippocampal BDNF Expression Related to Epigenetic Modifications in the Shank1 Knockout Mouse Model for Autism. Sungur, A Ozge; Jochner, Magdalena CE; Harb, Hani; Kilic, Ayse; Garn, Holger; Schwarting, Rainer KW; Wöhr, Markus.

5:52 Alcohol induced locomotor activity is mediated by dopamine D2-like receptors in zebrafish. Tran, Steven; Facciol, Amanda; Nowicki, Magda; Chatterjee, Diptendu; Gerlai, Robert.

6:00-7:00 ***Oral Session 1: Addiction.*** Chair: Wendy Adams. *Regina Ballroom 2*

6:00 Readers of histone acetylation marks regulate behavioral and transcriptional responses to drugs of abuse. Sartor, Gregory C.; Powell, Sam K.; Wahlestedt, Claes.

6:10 Ventral tegmental area L-type calcium channel mechanisms mediating cue-induced cocaine-seeking. Addy, Nii A; Nunes, Eric J; Hughley Shannon M; Solecki, Wojciech B; Wickham , Robert J; Small, Keri M; Rajadhyaksha, Anjali M.

6:20 Prenatal testosterone activity determines adult alcohol drinking and morphology in male and female mice. Huber, Sabine E.; Lenz, Bernd; Kornhuber, Johannes; Muller, Christian P.

6:30 Ceftriaxone and cocaine relapse: contrasting the roles of xCT and GLT-1 upregulation. Knackstedt, Lori.

6:40 Sex differences in the selection between psychostimulant and food reinforcement in rats. Kippin, Tod; Bagely, Jared; Purpura, Mari; Vieira, Philip.

6:50 Tetrahydrocannabivarins ? Cannabinoids with Strong Anti-Nicotine Effects in Multiple Rodent Models of Nicotine Dependence. Gardner, Eliot L.; Muldoon, Pretal; Wang, Xiao-Fei; Bi, Guo-Hua; Damaj, M. Imad; Lichtman, Aron H.; Pertwee, Roger G.; Xi, Zheng-Xiong.

6:00-7:00 ***Oral Session 2. Schizophrenia, other Genetic Disorders.*** Chair: Andrew Gundlach. *Regina Ballroom 1*

6:00 Arc/Arg3.1 genetic disruption in mice causes dopamine system alterations and neurobehavioral phenotypes related to schizophrenia. Managò, Francesca; Mereu, Maddalena; Mastwal, Surjeet; Scheggia, Diego; Emanuele, Marco; Mastrogiacomo, Rosa; Talbot, Konrad; De Luca, Maria A.; Weinberger, Daniel R.; Wang, Kuan H.; Papaleo, Francesco.

6:10 Preventing both schizophrenia- and depression-like behavioral abnormalities in a novel neurodevelopmental model. Weiner Ina, Wolff Nizan, Ardeli Rachel, Jacobovich Elad, Doron Ravid.

6:20 Evaluating the validity of a novel transgenic mouse model for neuregulin 1 type III for schizophrenia. Tim Karl, Juan C Olaya, David Lloyd, Carrie L Heusner, Mitsuyuki Matsumoto & Cynthia Shannon Weickert.

6:30 A precision medicine genetic marker for core cognitive deficits in schizophrenia. Diego, Scheggia; Maddalena, Mereu; Marco, Armando; Maria, De Luca; Genny, Orso; Francesco, Papaleo.

6:40 The role of mesopontine cholinergic neurons in prepulse inhibition of startle. Azzopardi, Erin; Louttit, Andrea; Haddad, Faraj; Schmid, Susanne.

6:50 Hypoglycemia Reduces Cognitive Performance with Changes of Cerebral Blood Flow in Subjects with Type 1 Diabetes. Gjedde, Albert; Gejl, Michael; Brock, Birgitte; Møller, Arne; Van Duinkerken, Eelco; Haahr, Hanne; Hansen, Charlotte; Chu, Pei-Ling; Stender-Petersen, Kirstine; Rungby, Jørgen.

Thursday, June 9

8:00-10:00 ***Behavioral and molecular bases of drug and food addiction: Similarities and Differences.*** Chair: Jean Lud Cadet. *Regina Ballroom 2*

8:00 Compulsive palatable food eating in the presence of adverse consequences. Cadet, Jean Lud; White, Shannan; and Krasnova, Irina.

8:30 Molecular mechanisms underlying methamphetamine addiction and relapse. Krasnova, Irina.

9:00 Sign-tracking; A failure in flexibility. Helen M. Nasser, Yu-Wei Chen, Kimberly Fiscella Donna J. Calu.

9:30 Environmental enrichment and addiction. Solinas, Marcello.

8:00-10:00 ***Diet impact on brain plasticity and cognition.*** Chair: Guillaume Ferreira; Co-Chair: Patrizia Campolongo. *Regina Ballroom 1*

8:00 Juvenile obesity bidirectionally modulates amygdala and hippocampal memory systems. Ferreira Guillaume.

8:30 Effect of stress and high-fat diet on extinction memory and prefrontal plasticity in postweaning and adult animals. Mouna, Maroun; Guillaume, Ferreira; Rachel, Schayek; Tala, Khazen; Idit, Mor; Sophie, Trabish; Walaa Awad; Milly, Kritman.

9:00 Perinatal exposure to omega-3 fatty acid imbalance leads to enduring memory alterations in rats. Colucci, Paola; De Castro, Valentina; Peloso, Andrea; Campolongo, Patrizia.

9:30 The influence of diet and learning on the internal versus external controls of intake. Davidson, Terry.

10:00-10:30 **Exhibits – Refreshment Break.** *Regina Ballroom 3*

10:30 **Keynote: Klaus-Peter Lesch, PhD.**, University of Wuerzburg. Translating genetics findings into biological mechanisms for ADHD through animal models. *Regina Ballroom 1/2*

11:30-1:30 **Lunch.** *Salons*

11:30-1:30 **Career Development Workshop.** Chair: Julianne Jett. *Corvinus Salon*
All trainees are encouraged to attend. Friendly faculty members will participate in a "negotiations exercise" with trainees to educate them about issues to address when applying for jobs in the current competitive market, as well as enhance trainees' communication skills when discussing these pertinent topics. No matter where you are in your career trajectory or what your long-term career goals are, learning more about the art of negotiation will serve you well in your future success. Lunch will be provided for participants.

1:30-3:30 ***Reslilience Redux: Better living through neurobiological research.*** Chair: Kelly Lambert. *Regina Ballroom 2*

1:30 Does BDNF promote or prevent behavioral responses to social stress? Kim L. Huhman.

2:00 Stimulation of Entorhinal Cortex-Dentate Gyrus Circuitry is Antidepressive. Yun, Sanghee; Reynolds, Ryan P.; Rivera, Phillip D.; Segev, Amir; Ito, Naoki; Mukherjee, Shibani; Richardson, Devon R.; Kang, Catherine E.; Chetkovich, Dane M.; Kourrich, Said; Eisch, Amelia J.

2:30 Role of inflammatory factors and microRNAs in resilience to stress. Bhatnagar, Seema.

3:00 Who Moved My Cheese? Mapping resilient neurobiological response profiles to cognitive uncertainty and environmental threats. Lambert, Kelly.

1:30-3:30 ***Neuroendocrine Regulation of Animal Vocalization.*** Chair: Cheryl Rosenfeld; Co-Chair: Frauke Hoffmann. *Regina Ballroom 1*

1:30 Heeding the Hormonal Call: Turning on and Tuning in to Acoustic Signals. Andrew H. Bass.

2:00 Nonclassical actions of steroids in the modulation of vocal and auditory circuits in songbirds. Luke Remage-Healey.

2:30 Males mate call, females don't? Anuran vocal communication and its hormonal control. Hoffmann, Frauke.

3:00 Effects of bisphenol-A (BPA) on F2 Peromyscus californicus pup vocalizations. Johnson, Sarah A; Javurek, Angela B; Murphy, Claire R.; Khan, Zoya Z.; Conard, Caroline M.; Ellersieck, Mark R.; Hoffmann, Frauke; Schenk, A. Katrin; Rosenfeld, Cheryl S.

3:30-4:00 **Exhibits – Refreshment Break.** *Regina Ballroom 3*

4:00-5:00 ***Dopamine sensitization: A burden for treatments in schizophrenia?*** Chair: Davide Amato; Co-Chair: Anthony Vernon. *Regina Ballroom 2*

4:00 The acute and chronic effects of antipsychotic treatment on synaptic dopamine levels: Preliminary results from a meta-analysis of microdialysis studies. Joseph Kambeitz, Davide Amato.

4:20 Mechansims of antipsychotic treatment failure and psychosis. Amato, Davide; Canneva, Fabio; Kornhuber, Johannes; von Hörsten, Stephan; Müller, Christian, P.

4:40 Chronic antipsychotic treatment and grey matter volume loss: Epiphenomenon or cause for concern? Vernon, Anthony C.

4:00-5:00 ***TMS and Brain Functions*****.** Chair: José Rubén García Montes. *Regina Ballroom 1*

4:00 Basics and functional effects of transcranial electrical stimulation (tES). Michael A. Nitsche.

4:20 Exploring brain functions: TMS-EEG co-registration. Paolo Maria Rossini, Riccardo Di Iorio.

4:40 TMS to face dyskinesias in Parkinson's disease. René Drucker-Colín, José Rubén García Montes.

5:00-6:00 ***Stress and Behavior.*** Chair: Samina Salim. *Regina Ballroom 2*

5:00 Glutathione as a glutamate reservoir: The GLU that binds inflammation and neurotransmission. Sedlak, Thomas W.; Koga, Minori; Sawa, Akira.

5:15 A natural product as a tool to explore therapeutic targets for stress-induced microglial immune changes and depressive behaviors. Kamiya, Atsushi.

5:30 Oxidative Stress and Psychological Stress: A Cause or Consequence? Salim, Samina; Solanki, Naimesh.

5:45 The Role of Inflammation in PTSD and its Modulation by COMTVal158Met Genotype. Risbrough, Victoria; Deslauriers, Jessica; Nievergelt, Caroline; Baker, Dewleen; Geyer, Mark.

5:00-6:00 ***Pharmacological manipulation of trace amine-associated Receptor 1 signaling challenges conventional concepts of psychostimulant action.*** Chair: David Grandy; Co-Chair: Raul Gainetdinov. *Regina Ballroom 1*

5:00 Behavioral Consequences of Modulating Glutamate Transmission by TAAR1. Gainetdinov RR.

5:20 TAAR1 activation reduces cocaine intake and relapse: Behavioral and neurobiological evidence. Li, Jun-Xu.

5:40 Modulation of mouse behavior and cognition by the endogenous TAAR1 agonist 3-iodothyronamine. Zucchi, Riccardo.

6:00-6:30 **Exhibits – Refreshment Break.** *Regina Ballroom 3*

6:30-8:30 **Poster Session 1.** *Foyer 1*

1. The interaction of oxytocin and the vasopressin V1A receptor in reducing relapse to methamphetamine abuse. Everett, Nicholas; Baracz, Sarah; Cornish, Jennifer.
2. Single-Exposure Conditioned Place Preference: An animal model of initial subjective drug effects. Grisel, Judith.
3. Is there an implicit association between physical activity and alcohol consumption? Najjar, Laian; Neighbors, Clayton; Henderson, Craig; Young, Chelsie; Hoyt, Alex; Leasure, Jennifer.
4. Chronic Alcohol Drinking Alters Modulation of Dopamine Release in Rhesus Dorsal Striatum. Lovinger, David M., Salinas, Armando,Cuzon Carlson, Verginia, Mateo, Yolanda, Grant, Kathleen A.
5. Sex differences in the effects of naltrexone on appetitive and consummatory responses to ethanol in adult rats. Nieto, Steven J; Winoske, Kevin J; Kosten, Therese A.
6. Context-independent effects of footshock on drug-seeking. Pizzimenti, Christie; Navis, Thomas; Lattal, K. Matthew.
7. The role of behavioral contingency in excessive cocaine-induced escalation of intake. Ploense, Kyle; Vieira, Philip; Bubalo, Lana; Olivarria, Gema; Carr, Amanda; Kippin, Tod.
8. Prenatal testosterone activity determines adult alcohol drinking and morphology in male and female mice. Huber, Sabine E.; Lenz, Bernd; Kornhuber, Johannes; Müller, Christian P.
9. Prenatal alcohol exposure alters cranially directed blood flow and neurological responses to transient cerebral ischemia in adult mice. Bake, Shameena; Gardner, Rachael; Tingling, Joseph; Miranda, Rajesh C; Sohrabji, Farida.
10. Magnetic field stimulation diminishes the probability to increase dyskinesia and decreases FosB in the genetic and 6-OHDA models of Parkinson´s disease. Garcia-Montes, Jose-Ruben; Ruiz-DeDiego, Irene; Solis-Castrejon, Oscar; Drucker-Colin, Rene; Moratalla, Rosario.
11. Behavioral and molecular-biological characterization of a new rat substrain: relevance to neuropsychiatric disorders. Kekesi G., Ducza E., Büki A., Benedek G., Horvath G.
12. Effects of systemic administration of ibuprofen on stress response in a rat model of post-traumatic stress disorder. Bombi Lee, Insop Shim, Hyejung Lee, Dae-Hyun Hahm.

13. Gene variants in cytochrome P450 CYP2C19 and CYP2D6 are associated with psychosis in a clinical sample of persons with Down syndrome. Malt, Eva; Dahl, Renate; Juhasz, Katalin, Rud, Ellen; Haugsand, Trine; Davidsen, Eva.
14. Prenatal exposure to Intuerluekin-6: A translational study examining component behaviors and MR based metrics associated with ADHD and autism. Mills, Brian; Shunmugavel, Anandakumar; Pizzimenti, Christie; Lattal, Matt; Mitchell, Suzanne; Fair, Damien.
15. Neural response to cognitive and emotional empathy task in the brain of autism spectrum disorder. Jung-Woo, Son; Seungwon, Jung; LsboK, Lee; Hee-Rhee, Ghim.
16. The role of mesopontine cholinergic neurons in prepulse inhibition of startle. Azzopardi, Erin; Louttit, Andrea; Haddad, Faraj; Schmid, Susanne.
17. The Aid of Ephedrine HCL, Curcumin and Turmerone in Neurogenesis and Inhibition of Beta-Amyloid Plaques in Transgenic Mice Models. Paramasivam, Keerthi.
18. The therapeutic potential of cannabidiol for Alzheimer's disease. David Cheng, Andrew Jenner, Andrea Spiro, Brett Garner and Tim Karl.
19. Flumazenil effects on c fos expression in striatum of rats with associative tolerance to midazolam. Cruz-Morales SE, Gonzalez-Sanchez DJ, Castillo-Roberto G, Arriaga-Ramirez JPC.
20. Effects of GABA-B Receptor Modulation in a Model of Chronic Inflammation. Murtishaw, Andrew S.; Bolton, Monica M.; Heaney, Chelcie F., Langhardt, Michael A.; Belmonte, Krystal Courtney D.; Boren, Austin J.; Calvin, Kirsten N.; Kinney, Jefferson W.
21. Role for hypothalamic projections to habenula in obesity. Richard M. O'Connor and Paul J. Kenny.
22. Single neuron firing in the rat Amygdala and Piriform Cortex during Social Interaction. Pibiri, Francesca; Poulter, Steven; Lever, Colin.
23. Lanthionine synthetase C-like 2 protein (LANCL2) in the spinal cord is crucial to maintain normal nociceptive behaviors in rats. Han-Rong Weng and Dylan W. Maixner.
24. Critical developmental period for the effects of methamphetamine on social behavior of adult male and female rats. Hrebickova, Ivana; Sevcikova, Maria; Macuchova, Eva; Slamberova, Romana.
25. Hyper-locomotor activity in the mice lacking in an enzyme synthesizing chondroitin sulfate. Igarashi, Michihiro; Takeuchi, Kosei; Yoshioka, Nozomu; Takao, Keizo; Miyakawa, Tsuyoshi.
26. Social play behavior in juvenile rats after neonatal exposure to methamphetamine. Sevcikova, Maria; Holubova, Anna; Hrebickova, Ivana; Slamberova, Romana.
27. Changes in gut microbiome during development of behavioral sensitization to the dopamine agonist quinpirole. Szechtman, Henry; Jung, Tony; Jung, Paul; Raveendran, Lucshman; Farbod, Yasamin; Sakic, Boris; Dvorkin-Gheva, Anna; Surette, Michael.
28. Signaling by tuberoinfundibular peptide of 39 residues in the medial amygdala modulates male aggressive behaviors. Tsuda, Mumeko C; Usdin, Ted B.
29. Sex-dependent behavioral effects of isolation-rearing. Hall, F. Scott; Muskiewicz, Dawn; Joshi, Dankesh; Gutierrez, Federico Resendiz; Hall, Natasha; Saber, Yasir.
30. Mechanisms underlying the effects of Synthetic Psychoactive Cathinones. Hall, F. Scott; Issa, Omar; Muskiewicz, Dawn; Saber, Yasir; Hall, Natasha; Yager, Joseph; Osting, Taylor; Piao, Ying-Shan; Sora, Ichiro.
31. Harmonic resonances in EEG from human participants entrained to photic flicker. Thalheimer, William; Storrs, Tyler; Candelaria, Damien; Cocchieri, Caterina; Saia, Domenick; Da Silva, Brendha; Flores, Mary; Flores, Juan; Danbury, Michelle; Rossi III, John.
32. Convulsions induced by Methyl -carboline-3-carboxylate (-CCM) in mice: effects of preceding saline injections. Martin, Benot.
33. Dissociable roles for basolateral amygdala and orbitofrontal cortex in optimal choice behavior under conditions of reward variability. Alexandra Stolyarova, Alicia Izquierdo.
34. Behavioral characterization of neuropeptide S-deficient mice in animal paradigms of pathological fear. Kolodziejczyk, Malgortaza; Germer, Josephine; Kahl, Evelyn; Fendt, Markus.

35. Effects of lipopolysaccharide administration on performance deficits in the 5-choice serial reaction time task are augmented in socially-isolated rats. Adams, Wendy; Harris, Eva; Zeeb, Fiona; Taves, Matthew; Soma, Kiran; Winstanley, Catharine.
36. Effect of beta-asarone on impairment of spatial working memory and apoptosis in the hippocampus of rats exposed to chronic corticosterone administration. Bombi Lee, Insop Shim, Hyejung Lee, Dae-Hyun Hahm.
37. En route to delineating the hippocampal contributions to spatial learning. Poulter, Steven; Austen, Joe; Kosaki, Yutaka; Lever, Colin; McGregor, Anthony.
38. Relief learning requires a coincident activation of dopamine D1 and NMDA receptors within the nucleus accumbens. Bergado Acosta, Jorge R.; Kahl, Evelyn; Kogias, Georgios; Uzunezer, Taygun; Fendt Markus.
39. Aha-like experience in the rat. Makino, Kenichi; Ikegaya, Yuji.
40. Learning and memory in the traveling salesman problem in rats. Stojanovic, Marta; Blaser, Rachel.
41. Effects of Acute Ethanol Withdrawal and Intoxication on the Extinction and Reconditioning of Contextual Fear Memories. Williams, Amy R; Lattal, Kennon Matthew.
42. Withdrawn
43. Role of muscarinic acetylcholine signaling in G protein-coupled estrogen receptor-mediated social learning facilitation in female mice. Ervin, Kelsy; Qiu, Wansu; Topic, Tino; Choleris, Elena.
44. Long-term early life adverse experience affects recognition memory and accelerates the process of habituation to familiar environment. Holubova, Anna; Mikulecka, Anna; Pometlova, Marie; Nohejlova, Kateryna; Slamberova, Romana.
45. Learning impairments produced by embryonic lead exposure persisted in F3 male and female zebrafish. Xu, Xiaojuan; Weber, Daniel.
46. Post-weaning social isolation results in ultrasonic communication deficits, cognitive impairments and alterations in microRNA-dependent Ube3a1 function on neuronal plasticity in rodents: Implications for autism. Seffer, Dominik; Rippberger, Henrike; Valluy, Jeremy; Bicker, Silvia; Aksoy-Aksel, Ayla; Lackinger, Martin; Sumer, Simon; Fiore, Roberto; W?st, Tatjana; Metge, Franziska; Dieterich, Christoph; Schratt, Gerhard; Schwarting, Rainer K.W.; Wöhr, Markus.
47. Application of activation induced manganese-enhanced magnetic resonance imaging (MEMRI) for mapping of brain structures activated by operant behavior in rats. Gálosi, R., Szalay, Cs., Aradi, M., Pál, J., Perlaki, G., Karádi, Z. and Lénárd, L.
48. Temporal dissociation of activity-dependent alterations in prefrontal BDNF expression during decision-making shifts. Cole, Robert D.; Parikh, Vinay.
49. Exogenous ketone supplements reduce anxiety-related behavior in Sprague-Dawley and Wistar Albino Glaxo/Rijswijk rats. Ari, Csilla; Kovacs, Zsolt; Juhasz, Gabor; Murdun, Cem; Goldhagen, Craig R; Koutnik, Andrew; Poff, Angela M; Kesl, Shannon L; D'Agostino, Dominic P.
50. Long-term sexually-dichotomic impact of adolescent CRF hyper-signaling on adult anxiety-like traits and trauma susceptibility. Toth M, Desiree Hoppener, Geyer MA, Mansuy IM, Merlo-Pich E, Risbrough VB.
51. CB1 receptor antagonism increases anxiety-like behavioural responses and alters neurochemical levels in two distinct populations of zebrafish. Facciol, Amanda; Tran, Steven; Chatterjee, Diptendu; Gerlai, Robert.
52. The Cacna1c genetic rat model for affective disorders: Behavioral phenotypes and inflammatory markers. Braun, Moria D.; Kisko, Theresa M.; Kayumova, Rukshona; Raithel, Clara; Hohmeyer, Christine; Rietschel, Marcella; Witt, Stephanie H.; Schwarting, Rainer K.W.; Garn, Holger; Wöhr, Markus.
53. The impact of maternal separation on adolescent social behavior may be mediated by changes in the maternal care after separation. A. Magalhaes,R. Alves,M. Nogueira,C.J. Alves,A. Mesquita,T. Summavielle,L. De Sousa.
54. Environmental enrichment prevents autistic-like behaviors following early life stress in CD-1 Mice. Cornwell, Catherine; Melton, Christopher; McDowell, Yoanna; LeMon, Janelle.

55. Nucleus incertus, GABA and relaxin-3: an emerging modulatory role in arousal, stress and memory. Ma, Sherie; Ong-Palsson, Emma; Allocca, Giancarlo; Singleton, Caitlin; Williams, Spencer; Bathgate, Ross; Gundlach, Andrew.
56. Pharmacotherapy combined with psychotherapy in social disturbances: plastic role of the ventromedial prefrontal cortex. Mikics, Eva; Karpova, Nina; Biro, Laszlo; Guirado, Ramon; Miskolczi, Christina; Toth, Mate; Balazsfi, Diana; Zelena, Dora; Umemori, Juzoh; Haller, Jozsef; Castren, Eero.
57. Altruistic behavior in rats is enhanced by experience. Wrighten, Shayna; Kellis, Devin; Spears, Treonte.
58. The Neural Correlates of Visual Imagery. Winlove, Crawford I. P; Ranson, Jake; Aldworth, Susan; MacKisack, Matthew; Macpherson, Fiona; Onians, John; Zeman, Adam.
59. Early-life inflammation decelerates fear extinction in adult rodents? Potential implications for the endocannabinoid system. Doenni, Vienna M; Hill, Matthew N; Pittman Quentin J.
60. SERT on speed: Enhanced emission of amphetamine-induced 50-kHz ultrasonic vocalizations in rats lacking the serotonin transporter due to long-term adaptations in 5-HT2C receptor functioning. Kisko, Theresa M; Willadsen, Maria; Vörckel, Karl J; Seffer, Dominik; Schwarting, Rainer KW; Homberg, Judith; Wöhr, Markus.
61. Cortisol-signaling genes' DNA methylation changes due to early life stress assessed in peripheral tissues of adult male rhesus macaques. Nemoda, Zsofia; Massart, Renaud; Suderman, Matthew J.; Ruggiero, Angela M.; Suomi, Stephen J.; Szyf, Moshe.
62. Association between infant attachment behavior and DNA methylation of the glucocorticoid receptor gene promoter regions. Kruk, Emese; Lakatos, Krisztina; Őzéné, Lívia Kende; Bekecs, Boglárka; Tóth, Ildikó; Gervai, Judit; Nemoda, Zsófia.

Friday, June 10

8:00-10:00 ***Consequences of drugs and stress during adolescence: Today, Tomorrow, and Beyond.*** Chair: Elizabeth Byrnes; Co-Chair: Fair Vassoler. *Regina Ballroom 2*

8:00 The role of prefrontal norepinephrine in the ontogeny of cognitive control. McGaughy, Jill A.

8:30 Nicotine-induced synaptic plasticity in the orbitofrontal cortex differ between adolescent and adult mice. Turner, Jill.

9:00 Adolescent stress exposure increases vulnerability to addiction: Role of glutamate plasticity. Briand, Lisa; Fosnocht, Anne; Ellis, Alexandra; Deutschmann, Andre.

9:30 A history of adolescent morphine exposure induces transgenerational effects on reward and relapse. Vassoler, Fair.

8:00-10:00 ***Selected topics of the Hungarian Behavioral Neuroscience.*** Chair: László Lénárd; Co-Chair: Robert Gerlai. *Regina Ballroom 1*

8:00 Substance P and neurotensin: Reinforcers in the limbic system. Lénárd L., László K., Kertes E., Ollmann T., Péczely L., Kovács A., Gálosi, R., Karádi, Z.

8:20 The role of CRF and the urocortins in social interaction. Bagosi, Zsolt; Csabafi, Krisztina; Jászberényi, Miklós; Telegdy, Gyula.

8:40 Role of subcortical prefrontal projections in social behavior as revealed by axonal optic stimulation. Jozsef Haller, Eva Mikics, Laszlo Biro, Eszter Sipos, Dora Zelena, Mate Toth.

9:00 Glucose-monitoring neurons in the medial orbitofrontal cortex of rat. Szabo, Istvan; Hormay, Edina; Csetenyi, Bettina; Karadi, Zoltan.

9:20 The application of psychomotor vigilance measures in a nonhuman primate pharmacological model of neurocognitive disorders. Hernádi, István; Oláh, Vilmos; Trunk, Attila; Inkeller, Judit.

9:40 Neural mechanisms for vocal social perception: dog-human comparative fMRI studies. Attila Andics, Márta Gácsi, Tamás Faragó, Anna Gábor, Dóra Szabó, Ádám Miklósi.

10:00-10:30 **Exhibits – Refreshment Break.** *Regina Ballroom 3*

10:30 **Keynote Speaker: Henriette van Praag, PhD.**, National Institutes of Health. Regulation and Function of Adult Hippocampal Neurogenesis: the Role of Exercise. *Regina Ballroom 1/2*

11:30-1:30 **Lunch.** *Salons*

11:30-1:30 **Meet the Professionals.** Chair: Wendy Adams. *Corvinus Salon*
Pre-registration required for this event.

1:30-3:30 **Current progress in characterizing therapeutic strategies and challenges after experimental CNS injury.** Chair: Anthony E. Kline; Co-Chair: Corina O. Bondi. *Regina Ballroom 2*

1:30 Unraveling frontal lobe dysfunction after TBI with pre-clinical models. Bondi, Corina; Cooley, Emma; Rohac, Rebecca; Marshall, Ian; McPeake, Emily; Kutash, Lindsay; LaPorte, Megan; Cheng, Jeffrey; Kline, Anthony.

2:00 Using circuit-directed behavioral induction of immediate early genes as a biomarker for circuit integrity during recovery of brain injury. Thomas, Theresa; Khodadad, Aida; Adelson, P. David; Lifshitz, Jonathan.

2:30 CRHR1 Mediation of neuroplasticity and neuroinflammation in the hippocampus following global cerebral ischemia. Patricia B. de la Tremblaye and Hélène Plamondon.

3:00 When behavioral management after brain trauma goes awry. Kline, Anthony E, Bondi, Corina O.

1:30-3:30 ***The heterogeneity of depression: Obstacle or opportunity?*** Chair: Bill Deakin; Co-Chair: Gabriella Juhasz. *Regina Ballroom 1*

1:30 The role of comorbid disorders in deciphering the pathophysiology of depression. Juhasz, Gabriella; Marx, Peter; Antal, Peter; Deakin, Bill.

2:00 Can we translate the diathesis-stress approach from animal to human research? Harro, Jaanus; Kaart, Tanel; Laas, Kariina; Veidebuam, Toomas.

2:30 Stratification of Appetite Changes in Depression and in Response to Anorectic Drugs using functional Magnetic Resonance Imaging. Dourish, Colin.

3:00 Exploring possible stratifications using a Bayesian systems-based approach in large-scale heterogeneous data. Hullam, Gabor; Juhasz, Gabriella; Antal, Peter.

3:30-4:00 **Exhibits – Refreshment Break.** *Regina Ballroom 3*

4:00-5:00 ***The different faces of hippocampal theta.*** Chair: Colin Lever. *Regina Ballroom 2*

4:00 Spatial cognition or Anxiety? Can dissociable theta frequency correlates reconcile opposing views of hippocampal function? Colin Lever, Miranda Hines, Steven Poulter, Vincent Douchamps, Anthony McGregor.

4:15 Coding of space and time by interactions of entorhinal cortex and medial septum. Hasselmo, Michael.

4:30 What does hippocampus tell hypothalamus? Optogenetic control of hippocampal theta oscillations reveals their function in locomotion. Bender, Franziska; Gorbati, Maria; Carus-Cadavieco, Marta; Denisova, Natalia; Gao, Xiaojie; Holman, Constance; Ponomarenko, Alexey; Korotkova, Tatiana.

4:45 Theta-related physiology in the freely moving developing rat. Thomas J Wills.

4:00-5:00 ***Role of the prefrontal cortex and hippocampus in motivation, decision making, and drug relapse: Cooperation or competition?*** Chair: Jennifer M. Bossert. *Regina Ballroom 1*

4:00 My ERK-some PFC: A glutamatergic basis for incubated drug-craving. Szumlinski, Karen K.

4:15 Role of projections from ventral subiculum to nucleus accumbens shell in context-induced reinstatement of heroin seeking in rats. Bossert, Jennifer M.; Adhikary, Sweta; St. Laurent, Robyn; Marchant, Nathan J.; Wang, Huiling; Morales, Marisela; Shaham, Yavin.

4:30 Prefrontal cortex and hippocampus: henchmen of addiction. Fuchs, Rita A.

4:45 Hippocampal circuits in cognition and behavior. Chudasama, Yogita.

5:00-6:00 ***Oral Session 3. Learning, Memory, Attention, and Related Cognitive Functions.*** Chair: F. Scott Hall. *Regina Ballroom 2*

5:00 In vivo optogenetic manipulation of dopamine neurons in a novel behavioral economics based food-seeking task. Oleson, Erik; Pultorak; Katherine; Krzystyniak, Gregory; Das, Raibatak; Schelp, Scott.

5:15 ERK phosphorylation of cholinergic medial septal neurons by icv infusion of a relaxin3 agonist impairs spatial working memory. Francisco E. Olucha-Bordonau, Héctor Albert-Gascó, Álvaro García-Avilés, Salma Moustafa, Sandra Sánchez-Sarasua, Andrew L. Gundlach, Ana M. Sánchez-Pérez.

5:30 The Aid of Ephedrine HCL, Curcumin and Turmerone in Neurogenesis and Inhibition of Beta-Amyloid Plaques in Transgenic Mice Models. Paramasivam, Keerthi.

5:45 The sound of silence - The role of vocalizations in sociosexual behaviors and mate choice in groups of rats (Rattus Norvegicus) in a seminatural environment. Xi Chu, Anders Agmo.

5:00-6:00 ***New cellular insights into the maintenance of memory in mammals and mollusks.*** Chair: David Glanzman. *Regina Ballroom 1*

5:00 PKMzeta, LTP and Memory. Sacktor, Todd.

5:15 PKM stabilizing proteins in long-term memory. Ferguson, Larissa; Chen, Shanping; Glanzman, David; Sossin Wayne.

5:30 Multiple Calpains Can Mediate Formation of Protein Kinase Ms Involved in Memory-Related Synaptic Plasticity. Hastings, Margaret H.; Abi Farah, Carole; Dunn, Tyler W.; Hu, Jiangyuan; Cai, Diancai; Chen, Shanping; Gong, Katrina; Fan, Xiaotang; Bougie, Joanna K.; Baker-Andresen, Danay; Schacher, Samuel; Glanzman, David L.; Sossin, Wayne S.

5:45 The role of PKM and epigenetic mechanisms in the consolidation and maintenance of long-term memory. Glanzman, David L.; Chen, Shanping; Cai, Dianbai; Pearce, Kaycey; Roberts, Adam C.

6:00-6:30 **Exhibits - *Refreshment Break.*** *Regina Ballroom 3*

6:30-8:30 **Poster Session 2.** *Foyer 1*

1. A novel oxytocin-like compound reduces motivation to self-administer methamphetamine and relapse to methamphetamine seeking in rats. Baracz, Sarah; Everett, Nicholas; Bowen, Michael; Kassiou, Michael; Cornish, Jennifer; McGregor, Iain.
2. Effect of Bupleurum falcatum on behavioral sensitization and enhanced dopaminergic expression. Dae-Hyuk Jang, Hyun-ju Lee; Dae-Hyun Hahm, Hye-Jung Lee; Insop Shim.
3. Potential role of wolfberry extract in the drug abuse rehabilitation: Protective effect of Lycium barbarum polysaccharide on dextromethorphan-induced neurogenesis and mood impaired rats. Po, Kevin Kai-ting; Siu, Andrew Man-hong; Chan Jackie Ngai-man; So, Kwok-fai; Fung Kai-hang; Lau, Benson Wui-man.
4. Determining Mechanisms behind the Blunted Response to Stimulants in Toxoplasma gondii Chronically Infected Mice. McFarland, Ross; Weng, Zi Teng; Sibley, David; Baraban, Jay; Yolken, Robert; Pletnikov, Mikhail.
5. The role of mGluR5 in neurobiological mechanisms of resilience to develop comorbid PTSD and cocaine addiction. Marek Schwendt and Lori Knackstedt.
6. Mapping of the prenatal and adult methamphetamine effects on D1-like dopamine, M1 and M2 muscarinic receptors in rat central nervous system. Slamberova, Romana; Farar, Vladimir; Valuskova, Paulina; Myslivecek, Jaromir.
7. Altered long-term platicity of glutamatergic synapses in the nucleus accumbens of alcohol-dependent rats. Giuseppe Talani, Gabriele Sarigu, Laura Firino, Francescangelo Vedele, Luca Picci, Giovanni Biggio, Enrico Sanna.
8. Alcohol induced locomotor activity is mediated by dopamine D2-like receptors in zebrafish. Tran, Steven; Facciol, Amanda; Nowicki, Magda; Chatterjee, Diptendu; Gerlai, Robert.
9. The role of copa and CB1 receptor in cocaine-induced locomotor sensitization and JWH-210-induced dopamine release. Jaesuk Yun, Tac-hyung Lee, Young-Hoon Kim, HyeJin Cha , Hye-Kyung Park and Hyung Soo Kim.
10. Ceftriaxone and cocaine relapse: contrasting the roles of xCT and GLT-1 upregulation. Knackstedt, Lori.
11. Examining the effect of chronic intranasal oxytocin administration on the neuroanatomy and behaviour in two different autism-related mouse models. Buchwald, Zsuzsa; Stuive, Monique; Ellegood, Jacob; Anagnostou, Evdokia; Lerch, Jason.
12. Mild Behavioural Impairments in Shank3 Mutant Mice, a mouse model for autism spectrum disorders? Allain-Thibeault Ferhat, Anne-Marie Le Sourd, Thomas Bourgeron, Elodie Ey.
13. Heterozygous deletion of GTF2i results in hypersocial behavior, but duplication of this gene has no effects on social behavior in mice: implications for Williams Beuren Syndrome and Autism Spectrum Disorder. Martin, Loren; Iceberg, Erica; Allaf, Gabriel; Slama, Maryann; Liew, Cassandra; Engelmann, Julie.
14. Developmental social isolation alters expression of neural proteins in adult zebrafish. Shams, Soaleha; Chatterjee, Diptendu; Gerlai, Robert.

15. Deficiency of neurogranin, a susceptible gene for schizophrenia, causes behavioral phenotypes related to schizophrenia and immaturity of the dentate gyrus in mice. Satoko Hattori, Hideo Hagihara, Yoshihiro Takamiya, Toshiki Kameyama, Yuya Ouchi, Hidehito Inagaki, Hiroki Kurahashi, Freesia L Huang, Kuo-Ping Huang, Tsuyoshi Miyakawa.
16. Aberrant Cognitive Phenotypes and Altered Hippocampal BDNF Expression Related to Epigenetic Modifications in the Shank1 Knockout Mouse Model for Autism. Sungur, A Ozge; Jochner, Magdalena CE; Harb, Hani; Kilic, Ayse; Garn, Holger; Schwarting, Rainer KW; Wöhr, Markus.
17. A precision medicine genetic marker for core cognitive deficits in schizophrenia. Diego, Scheggia; Maddalena, Mereu; Marco, Armando; Maria, De Luca; Genny, Orso; Francesco, Papaleo.
18. Stimulation of the nucleus pontis oralis elicits low frequency oscillations at different frequencies in the prefrontal cortex and hippocampus in urethane anesthetized rats. Bernat Kocsis.
19. CRHR1 Mediation of neuroplasticity and neuroinflammation in the hippocampus following global cerebral ischemia. Patricia B. de la Tremblaye and Hélène Plamondon.
20. Dopaminergic nature of behaviorally-induced emission of 50 kHz appetitive vocalizations. Mulvihill, KG; Brudzynski, SM.
21. The antidepressant-like effect of agmatine is associated with AMPA receptor activation and increased levels of BNDF and synaptic proteins in prefrontal cortex. Neis, Vivian B; Moretti, Morgana; Bettio, Luis Eduardo; Ribeiro, Camille; Rosa, Priscila; Gonzalves, Filipe; Lopes, Mark; Leal, Rodrigo; Rodrigues, Ana Lucia.
22. Loss of neuronal activity in the central amygdala of seizure prone Fmr1 KO mice is conserved across multiple mouse lines susceptible to audiogenic seizures. Davenport, Matthew; Robinson, Chandler; Grainger, Lindsey; King, Andrew; Erickson, Craig; Schaefer, Tori.
23. Investigating the effects of history of concussion on baseline scores on the Sport Concussion Assessment Tool (SCAT-2). Kim M Gerecke; Madeline Davis.
24. An investigation of maternal experience on neurobiological and behavioral responses in middle aged rats. Kirk, Emily; Thompson, Brooke; Barha, Cindy; Galea, Liisa; Bardi, Massimo; Kent, Molly; Lambert, Kelly.
25. Strains of an accompanying conspecific affect the efficacy of social buffering in male rats. Kiyokawa, Yasushi; Nakamura, Kayo; Takeuchi, Yukari; Mori, Yuji.
26. Ketamine exposure during adolescence increases sensitivity to reward-related stimuli in adulthood. Riggs, Lace M.; Alipio, Jason B.; Garcia, Israel; Zavala, Arturo R.; Iniguez, Sergio D.
27. Prodynorphin genetic polymorphisms and ventral striatonigral pathway activity contribute to individual differences in novelty seeking and positive reward traits. Egervari, Gabor; Jutras-Aswad, Didier; Landry, Joseph; Miller, Michael; Anderson, Sarah Ann; Michaelides, Michael; Jacobs, Michelle; Peter, Cyril; Yiannoulos, Georgia; Liu, Xun; Hurd, Yasmin L.
28. An open source toolkit for combining neurophysiology and rodent behavior. Katalin Sviatkó, Tamás Laszlovszky, Panna Hegedüs, Nicola Solari, Joshua I Sanders, Balázs Hangya.
29. Integrity of Parent's Brain in Infancy Supports the Development of Children's Social Competencies. Abraham, Eyal; Hendler, Talma; Feldman, Ruth.
30. Elevated blood ketone levels increase the latency of anesthetic induction in GLUT1 mouse model. Ari, Csilla; Murdun, Cem; Goldhagen, Craig; Rogers, Christopher; D`Agostino, Dominic.
31. Individual differences in fear extinction; Role of orexin and cholinergic systems. Wilson, Marlene A.; Sharko, Amanda C; Kaigler, Kris F; Mott, David; McElroy, Joshua; Hartshorn, George; Fadel, Jim R.
32. The subunit-specific role of NMDA receptors in behavioral dysfunctions evoked by traumatic event. Laszlo, Biro; Eva, Mikics; Eszter, Sipos; Christina, Miskolczi; Mate, Toth; Jozsef, Haller.
33. High fat diet induced neuroinflammation and cognitive impairment can be restored by fitohormone abscisic acid treament. SanchezPerez, Ana Maria; Sanchez, Sandra; Moustafa, Salma; Garcia-Aviles, Avaro; OluchaBordonau Francisco.

34. The memory-promoting effects of estradiol and low luteinizing hormone: Possible role of brain-derived neurotrophic factor. Thornton, Janice; Bohm-Levine, Nathaniel.
35. Do prenatally methamphetamine-exposed male and female rats differ in the effect of chronic treatment with various drugs on spatial learning? Macuchova, Eva; Hrebickova, Ivana; Sevcikova, Maria; Nohejlova, Kateryna; Slamberova, Romana.
36. Rat model of prenatal malnutrition: prefrontal cortical dysfunction and neuropsychiatric implications. McGaughy, Jill A.; Galler, Janina R.
37. Acute amphetamine administration improves attention in rats with low baseline performance. Turner, Karly; Peak, James; Burne, Thomas.
38. Dorsal hippocampal dopamine D2-type receptors sex-specifically mediate the social transmission of food preferences in mice. Matta, Richard; Underwood, Emily A.; Leach, Zoe K.; Vertes, Alex C.; Atabakhsh, Victoria; da Silva, Mayara B.; Choleris, Elena.
39. Gender Differences in Decision-Making under Risk. Cherkasova M. V., Winstanley C. A., Clark L., Stoessl A.J.
40. Exploring Neurobiological Markers of Resilience Through Life's Ups and Downs: Effects of Contingency Training in Male and Female Long-Evans Rats. Kent Molly, Scott Samantha, Mckearney Noelle, Dozier B, Lambert Skylar, Terhunecotter Brennan, Kirk Emily, Thompson Brooke, Bardi Massimo, & Lambert Kelly.
41. Resilience Therapy for Depression: Exploring Neurobiological Adjustments to Predisposed and Acquired Behavioral Strategies. McKearney, Noelle; Dozier, Braeshawn; Lambert, Skylar; Scott, Samantha; Kent,Molly; Bardi, Massimo; Lambert, Kelly.
42. The impact of neurogenesis on flexible maze training: effects on hippocampal volume and cognition. Schoenfeld, Timothy; Rhee, Diane; Cameron, Heather.
43. Exploring the Causal Link Between Ultrasonic Vocalizations and Behavior in Rats. Burke, Candace; Kisko,Theresa; Pellis, Sergio; Euston, David.
44. Wogonin attenuates hippocampal neuronal loss and cognitive dysfunction in trimethyltin-intoxicated rats. Sunyoung Lee, Bombi Lee; Insop Shim, Hyejung Lee; Dae-Hyun Hahm.
45. Relaxin-3/RXFP3 signalling and anxiety: effects of chronic rAAV expression of an RXFP3 agonist peptide in ventral hippocampus. Rytova, Valeria; Ganella, Despina; Hawkes, David; Bathgate, Ross; Ma Sherie; Gundlach, Andrew.
46. The putative lithium-mimetic ebselen reduces impulsive action but not impulsive choice. Barkus, Chris; Ferland, Jacqueline-Marie; Adams, Wendy; Bannerman, David; Winstanley, Catherine; Sharp, Trevor.
47. The Activation And Blockage Of Crf Type 2 Receptors Of The Medial Amygdala Alter Elevated T-Maze Inhibitory Avoidance, An Anxiety-Related Response. Viana, Milena B.; Alves, Stephanie W.E.; Portela, Natasha C.; Silva, Mariana S.; C?spedes, Isabel C.; Bittencourt, Jackson C.
48. A gene x environment mouse model of switching between affective states: Reducing DAT function results in hypersensitivity to seasonal photoperiod-induced changes in affect. Cope, Zackary A; Dulcis, Davide; Young, Jared W.
49. Adaptations of the dorsal raphe in a rat model of depression and following antidepressant treatment. Babb, Jessica A; Linnros, Sofia E; Commons, Kathryn G.
50. Exposure to a selective-serotonin reuptake inhibitor (SSRI) during pregnancy impacts sensitization to cocaine in a sex-dependent manner. Kott, J. M., Mooney-Leber, S. M., Perrine, S., & Brummelte, S.
51. Individual variability in mice? response to lithium: a hurdle or an advantage? Itamar Ezer, Catherine Belzung, Haim Einat.
52. Subdiaphragmatic vagotomy does not influenced rats? behavior in elevated plus maze and does not protect against noradrenergic responses after i.p. LPS injection. Marek Wieczorek, Anna Kobrzycka, Krystyna Koziec, Artur H. Swiergiel, Marta Siudak.
53. Changes of neuronal plasticity in the hippocampus of mothers induced by 3h pups separation during the first two weeks after birth. Mostallino, Maria Cristina; Biggio, Francesca; Boi, Laura; Biggio, Giovanni.

54. The role of Mitogen and Stress activated protein Kinase 1 in response to environment enrichment throughout life. Lorenzo Mor?1, J. Simon Arthur and Bruno Frenguelli
55. Does aberrant hippocampal neurogenesis affect rat?s behavior in different behavioral tests? Costa, Ana Paula Ramos; Levone, Brunno Rocha; Linartevichi, Vagner Fagnani; Vanz, Felipe; Boutaud, Claudia Ailinne Vera; Valenzuela, Camila Mariel Quinones, Lino de Oliveira, Cilene; Dinan, Thimoty G.; O'leary, Olivia; Cryan, John F.; de Lima, Thereza C.
56. Adult hippocampal neurogenesis affects motivation to obtain sucrose, but not food, reward in operant tasks. Karlsson, Rpse-Marie; Wang, Alice; Sonti, Anup; Cameron, Heather.
57. Effect of venlafaxine and chronic unpredictable stress on behavior and hippocampal neurogenesis of rat dams. Melichercikova, Kristina; Csaszar, Eszter; Ujhazy, Eduard; Mach Mojmir; Dubovicky, Michal.
58. Socio-sexual behaviors in ovariectomized rats housed in a seminatural environment and treated with the estrogen receptor α agonist propylpyrazoletriol (PPT) or the estrogen receptor β agonist diarylpropionitrile (DPN). Olivia Le Moëne, Anders Ågmo.
59. How many synapses does a single microglia monitor in the stratum radiatum of CA1? Krejčova, Lane Viana; Bento-Torres,J.; Guedes, Rubem CA; Oliveira, Marcus; Perry, Victor Hugh; Picanço-Diniz, Cristovam.
60. Androgen receptor overexpression leads to deficits in fear-conditioning in male mice. Ramzan, Firyal; Azam, Amber; Monks, Ashley; Zovkic, Iva.
61. Using circuit-directed behavioral induction of immediate early genes as a biomarker for circuit integrity during recovery of brain injury. Thomas, Theresa; Khodadad, Aida; Adelson, P. David; Lifshitz, Jonathan.
62. Investigation of sucrose preference in large home cage with environmental enrichment. Kekesi, Gabriella; Ducza, Eszter; Büki, Alexandra; Benedek, Gyorgy, Horvath, Gyongyi.
63. AMBITUS system, a rectangular corridor for the investigation of cognitive function. Horvath G., Liszli P., Kekesi G., Büki A., Benedek G.

Saturday, June 11

8:00-10:00 ***Individual vulnerability to addiction: Dissection of behavior, neural circuits, cellular and molecular mechanisms.*** Chair: Gabor Egervari; Co-Chair: Yasmin Hurd. *Regina Ballroom 2*

8:00 Inter-individual differences in cocaine and heroin addiction in the rat: behavioural and neurobiological mechanisms. Belin, D.

8:30 When the brakes fail: mPFC plasticity mechanisms in drug seeking. De Vries, Taco.

9:00 Contribution of genetic and environmental factors in the regulation of stress mechanisms and individual vulnerability to drugs of abuse. Ciccocioppo, Roberto; Domi, Esi; Scuppa Giulia; Brunori, Gloria, Shen, Quienwei; Ubaldi, Massimo.

9:30 Prodynorphin genetic polymorphisms and ventral striatonigral pathway activity contribute to individual differences in novelty seeking and positive reward traits. Egervari, Gabor; Jutras-Aswad, Didier; Landry, Joseph; Miller, Michael; Anderson, Sarah Ann; Michaelides, Michael; Jacobs, Michelle; Peter, Cyril; Yiannoulos, Georgia; Liu, Xun; Hurd, Yasmin L.

8:00-10:00 ***Integrated neuromodulatory control of arousal and complex behaviours: Focus on dual transmitter systems and networks.*** Chair: Sherie Ma; Co-Chair: William Wisden. *Regina Ballroom 1*

8:00 Histamine and GABA co-transmission promote arousal. Wisden, William; Yu, Xiao; Ye, Zhiwen; Houston, Cat; Harding, Edward; Brickley, Stephen G; Franks, Nicholas P.

8:30 Interactions of glutamate/orexin and GABA/MCH systems with arousal networks. Leonard, Christopher S.

9:00 Central cholinergic neurons are rapidly recruited by reinforcement feedback. Hangya, Balazs; Ranade, Sachin; Lorenc, Maja; Kepecs, Adam.

9:30 Nucleus incertus, GABA and relaxin-3: an emerging modulatory role in arousal, stress and memory. Ma, Sherie; Ong-Palsson, Emma; Allocca, Giancarlo; Singleton, Caitlin; Williams, Spencer; Bathgate, Ross; Gundlach, Andrew.

10:00-10:30 **Exhibits - *Refreshment Break.*** *Regina Ballroom 3*

10:30 **Keynote Speaker. Urs Meyer, PhD.**, University of Zurich – Vetsuisse. Developmental Neuroinflammation and Long-Term Brain Pathology: From Models and Mechanisms to Transgenerational Effects. *Regina Ballroom 1/2*

11:30-1:30 **Lunch.** *Salons*

1:30-3:30 ***Exploring novel systems involved in the aetiology and potential treatment of anxiety disorders.*** Chair: David Slattery; Co-Chair: Clara Perani. *Regina Ballroom 2*

1:30 Assessing the role of oxytocin and neuropeptide S in anxiety-related behaviour. Slattery, David; Jurek, Ben; Martinetz, Stefanie; Grund, Thomas; Neumann, Inga.

2:00 Marijuana as Medicine: Targeting cannabinoid-modulating circuits to treat anxiety. Holmes, Andrew.

2:30 Stress exposure and High-Fat diet alter maternal anxiety-related behaviour and hypothalamus-pituitary-adrenal axis function. Perani, Clara; Hillerer, Katharina; Neumann, Inga; Slattery, David.

3:00 The microbiota-gut-brain axis as a novel strategy for targeting anxiety disorders. Cryan, John. F.

1:30-3:30 ***Developmental rodent models of behavioral dysfunction in neuropsychiatry: Disrupting the excitatory/inhibitory balance.*** Chair: Jared Young; Co-Chair: Susan Powell. *Regina Ballroom 1*

1:30 Rat model of prenatal malnutrition: prefrontal cortical dysfunction and neuropsychiatric implications. McGaughy, Jill A.; Galler, Janina R.

2:00 Cognition, glutamate, and developmental vitamin D-deficiency in rodents. Burne, Thomas,McGrath, John ,Turner, Karly.

2:30 Effects of perinatal and adolescent oxidative stress on inhibitory interneurons and behavior in mice. Powell, Susan; Khan, Asma; de Jong, Loek; Kamenski, Mary; Higa, Kerin; Lucero, Jacinto; Young, Jared; Behrens, M. Margarita.

3:00 Reducing neuronal transcription factor Sp4 alters glutamatergic/NMDA receptor function and behaviors relevant to serious mental illness. Jared W. Young and Xianjin Zhou.

3:30-4:00 **Exhibits - *Refreshment Break.*** *Regina Ballroom 3*

4:00-5:00 ***Function and neuroplasticity in the mesocorticolimbic system and alcohol dependence.*** Chair: Giovanni Biggio; Co-Chair: David M. Lovinger. *Regina Ballroom 2*

4:00 Synaptic Adaptations in the Dorsal Striatum and their Role in Alcohol-Related Habits. Lovinger, David M.

4:12 Dopaminergic hypofunction in alcohol dependence: from rodents to humans. Diana, Marco.

4:24 Altered long-term plasticity of glutamatergic synapses in the nucleus accumbens of alcohol-dependent rats. Sanna, Enrico; Licheri, Valentina; Sarigu, Gabriele; Biggio, Giovanni; Talani, Giuseppe.

4:36 Acute and long-lasting changes in neurotransmission in rat striatal subregions by ethanol. Adermark, Louise.

4:48 GABA-A drugs, addiction and neuroplasticity. Korpi, Esa R.; Vashchinkina, Elena

4:00-5:00 ***Colliculo-pulvinar pathway: The fast and coarse road for biologically relevant stimuli in primates.*** Chair: Rafael Maior. *Regina Ballroom 1*

4:00 Emotion perception without visual cortex: functional and anatomical mechanisms. Marco Tamietto, Alessia Celeghin.

4:15 Interaction between the primate deep layers of superior colliculus and the amygdala: Behavioral effects and anatomical connections. Malkova, Ludise; Saunders, Richard C.; Forcelli Patrick A.

4:30 Of friends and foes: Threat detection at the ontogenesis of social cognition. Maior, Rafael; Tomaz, Carlos.

4:45 Rapid detection of snakes and faces in the monkey superior collicular and pulvinar neurons in the subcortical visual pathway. Nishimaru, Hiroshi; Le, Quan Van; Nguyen, Minh Nui; Matsumoto, Jumpei; Takamura, Yusaku; Ono, Taketoshi; Nishijo, Hisao.

5:00-6:00 ***Oral Session 4. Affective Disorders.*** Chair: Corina Bondi. *Regina Ballroom 2*

5:00 Gestational stress and fluoxetine treatment differentially affect plasticity, methylation and serotonin levels in the PFC and hippocampus of the rat dam. Pawluski, Jodi; Rayen, Ine; van Donkelaar, Eva; Loftus, Tiffany; Steinbusch, Harry; Kokras, Nikolaos; Dalla, Christina; Gemmel, Mary.

5:10 Positive reinforcing and anxiolytic effects of oxytocin microinjection in the rat central nucleus of amygdala. Laszlo, Kristof; Kovacs, Anita; Zagoracz, Olga; Ollmann, Tamas; Peczely, Laszlo; Kertes. Erika; Karadi, Zoltan; Lenard, Laszlo.

5:20 Corticosterone induces depressive-like behavior in juvenile female post-pubescent rats, but not pre-pubescent rats. Tyler R. Nickle, Erica M. Stanley, Teresa J. Meyer, and David S. Middlemas.

5:30 Sex-dependent behavioral effects of isolation-rearing. Hall, F. Scott; Muskiewicz, Dawn; Joshi, Dankesh; Gutierrez, Federico Resendiz; Hall, Natasha; Saber, Yasir.

5:40 Individual variability in mice response to lithium: A hurdle or an advantage? Itamar Ezer, Catherine Belzung, Haim Einat.

5:50 Integrity of Parent's Brain in Infancy Supports the Development of Children's Social Competencies. Abraham, Eyal; Hendler, Talma; Feldman, Ruth.

5:00-6:00 ***Oral Session 5. Other Systems and Behavioral Effects.*** Chair: Irina Krasnova. *Regina Ballroom 1*

5:00 Exploring the Causal Link Between Ultrasonic Vocalizations and Behavior in Rats. Burke, Candace; Kisko,Theresa; Pellis, Sergio; Euston, David.

5:10 Closed nest pre-weaning environment improves the development of physical characteristics and reflexes in neonatal hypoxic ischemic injury. Donaldson, S. Tiffany; Rollins, Laura Grace; Santolucito, Hayley; Ravenelle, Rebecca; Mason, Briana.

5:20 The putative lithium-mimetic ebselen reduces impulsive action but not impulsive choice. Barkus, Chris; Ferland, Jacqueline-Marie; Adams, Wendy; Bannerman, David; Winstanley, Catherine; Sharp, Trevor.

5:30 Early-life inflammation decelerates fear extinction in adult rodents ? Potential implications for the endocannabinoid system. Doenni, Vienna M; Hill, Matthew N; Pittman Quentin J.

5:40 Pharmacotherapy combined with psychotherapy in social disturbances: plastic role of the ventromedial prefrontal cortex. Mikics, Eva; Karpova, Nina; Biro, Laszlo; Guirado, Ramon; Miskolczi, Christina; Toth, Mate; Balazsfi, Diana; Zelena, Dora; Umemori, Juzoh; Haller, Jozsef; Castren, Eero.

5:50 Application of activation induced manganese-enhanced magnetic resonance imaging (MEMRI) for mapping of brain structures activated by operant behavior in rats. Gálosi, R., Szalay, Cs., Aradi, M., Pál, J., Perlaki, G., Karádi, Z. and Lénárd, L.

6:00 **Early Career Award Presentation. Michael Bowen**, School of Psychology, University of Sydney, Australia. Department of Behavioral and Molecular Neurobiology, University of Regensburg, Germany. Faculty of Pharmacy, University of Sydney, Australia. Oxytocin inhibits ethanol consumption and intoxication in rats: interactions with dopamine and extrasynaptic GABA-A receptors. Bowen, Michael; Peters, Sebastian; Absalom, Nathan; Chebib, Mary; Neumann, Inga; McGregor, Iain. *Regina Ballroom 1*

6:30-7:30 **IBNS Business Meeting** – all members are requested to attend. *Corvinus Salon*

8:00-12:00 **Awards Ceremony and Banquet.** Join us for an evening of networking, music and dancing. Theme: Silver Anniversary (Silver & Black Attire). *Regina Ballroom 1/2/3*

Sunday, June 12

Departures

ABSTRACTS

Wednesday, June 8

8:00-10:00 ***Sex differences in the brain: Implications for behavioral and biomedical research.***
Chair: Elena Choleris.

Sex differences in rodent social behavior: hormonal influences. Choleris, Elena; Clipperton-Allen, Amy; Ervin, Kelsy SJ; Lymer, Jennifer M; Gabor, Christopher S; Sheppard, Paul; Phan, Anna. Department of Psychology and Neuroscience Program, University of Guelph, Guelph, ON, Canada. Sex differences in social behavior are well established and a hormonal influence has been repeatedly shown. Estrogens are known to affect behavior and cognition and they can do so both via delayed (hours-days), and longer lasting genomic mechanisms involving direct regulation of gene transcription by hormone receptors, as well as quick onset and rapid (minutes) mechanism that do not involve hormone receptor regulation of gene transcription. Over the years others and we have shown estrogenic regulation of multiple social behaviors in mice via both long term and rapid mechanisms. These include social learning, social recognition, and social interactions between strangers as well as cagemates. We and others have also been elucidating the role of the 3 main receptors for estrogens; estrogen receptor alpha (ER□), ER□ and the G protein-coupled ER (GPER). We are finding that different social behaviors respond differently to specific ER activation. For example, ER□ activation rapidly enhances social recognition while it does not affect social learning. In the case of a sexually different social behavior – agonistic interactions – we found that ER□ is implicated in both males and females but that its selective activation enhanced the sex-typical agonistic behaviors: overt aggressive attacks in males and dominance related behaviors in females. In addition, we sometimes find that the long term and rapid hormonal manipulations do not always yield the same results. For example, single-treatment, acute, activation of ER□ prolonged the expression of a socially learned food preference when administered 72 hr before testing (i.e. long term effect) whereas it did not affect social learning when administered 15 min before testing (i.e. rapid effects). Conversely, in other instances the long term and rapid manipulations of estrogen and ER action yield consistent results. For example, ER□ appears involved in social recognition in both long-term gene KO studies and in rapid studies with ER□ specific drugs. Finally, we are finding that while the hippocampus can drive many of the rapid effects of estrogens on social behavior, other areas currently under investigation (e.g. the Medial Amygdala) also appear to be involved. Overall ER-specific roles are being identified in the regulation of social behavior by estrogens and these may be reflected in the network of brain regions involved in each of these social behaviors. Supported by NSERC

Sex matters: Hippocampal neurogenesis, Spatial Learning and Pattern Separation. Liisa A.M. Galea. Department of Psychology, Program in Neuroscience and Centre for Brain Health, University of British Columbia, Vancouver, British Columbia, Canada, V6T 1Z4. Men and women differ in their vulnerability to develop neurodegenerative and neuropsychatric diseases. Many of these diseases are associated with cognitive disruptions and there are sex differences in the brain structures that are compromised with these diseases. For example, women are not only more likely to be diagnosed with Alzheimer's disease (AD) but cognitive deterioration with AD or mild cognitive impairment is worse in women compared to men. In addition, brain atrophy differs in women compared to men both in normal aging and with AD. The hippocampus produces new neurons throughout the lifespan in rodents and humans and adult neurogenesis plays a crucial role for pattern separation and for spatial long-term memory. However, it is important to establish how neurogenesis in the hippocampus may be involved in hippocampus-dependent cognition in both males and females given the sex differences in cognitive

disruptions following diseases that impact the hippocampus. Work in my laboratory has shown that there are sex differences, favoring males, in spatial navigation and pattern separation. We found that male spatial strategy users outperformed female spatial strategy users only when separating similar, but not distinct, patterns and typically males travel shorter distances to reach a hidden platform than females. Furthermore male spatial strategy users had greater neurogenesis in response to pattern separation training than all other groups consistent with findings in the Morris Water Maze showing that spatial training increased neurogenesis in males but not in females. Despite this, neurogenesis was positively correlated with performance on similar pattern trials during pattern separation in female spatial strategy users but negatively correlated with performance in male idiothetic strategy users. These results suggest that the survival of new neurons may play an important positive role for pattern separation of similar patterns in females. Consistent with these data, in the Morris Water Maze, spatial performance was positively related to the activation of new neurons in females but not males. These findings emphasize the importance of studying biological sex on hippocampal function and neural plasticity and have implications for neurodegenerative and neuropsychiatric disorders that target the hippocampus and affect cognition differentially in women versus men.

Estrogenic regulation of memory in males and females: Molecular mechanisms and implications for aging. Frick, Karyn M. University of Wisconsin-Milwaukee, Dept. of Psychology, Milwaukee, WI USA. The risks of age-related memory loss and dementia are greater in women than in men. Although estrogen loss at menopause likely plays a role, estrogen therapy is beneficial for cognition in only some menopausal women and exposes women to dangerous side effects including cancer and stroke. Reaping the beneficial effects of estrogens on memory without these side effects will require a more precise understanding of the molecular mechanisms through which estrogens regulate memory formation. This talk will summarize our laboratory's work in adult female mice identifying cell signaling pathways, epigenetic processes, and receptors in the dorsal hippocampus necessary for estradiol to enhance memory consolidation and/or increase hippocampal and prefrontal dendritic spine density. Implications of this work for age-related memory loss will be discussed.

Sex differences in stroke and stroke therapies. Farida Sohrabji. Texas A&M University Health Science Center, Department of Neuroscience and Experimental Therapeutics, Women's Health in Neuroscience Program, Bryan TX 77802. Stroke is the 4th leading cause of mortality and the leading cause of physical disability outside of war. The risk for stroke is affected by age and biological sex. Thus, at younger ages (< 45 years) more men are likely to get a stroke than women, but at older ages, stroke prevalence is greater among females than males. While this increased stroke risk among women may be due to greater longevity in this population, women are also more likely to have worse stroke outcomes as measured by increased mortality, longer hospitalization and transfer to assisted care facilities. Sex and age differences in stroke outcomes are well-modeled in preclinical animal studies as well. Young female rats and mice typically have small infarct volumes and attenuated loss of sensory motor performance as compared to age-matched males or middle aged females. Furthermore, aged female mice have worse outcomes as compared to aged males. A significant effort in preclinical stroke research focuses on identification of stroke neuroprotectants. While most studies are usually limited to the use of one sex, typically male, a growing number of recent studies have examined both male and female animals. Our recent studies have focused on miRNA, a class of non coding RNA, that act as translational repressors to determine their potential as stroke neuroprotectants. In the case of two miRNA, mir-Let-7f and mir363, manipulating these miRNA improves stroke outcomes in females but not males. These results support an emerging trend in preclinical stroke neuroprotectants that act in a sex-specific manner. Supported by NS074895 and AG042189

8:00-10:00 ***Epigenetic Regulation of Motivated Behaviors.*** Chair: Zuoxin Wang; Co-Chair: Mohamed Kabbaj.

Role of DNA methyl-cytosine oxidation in cocaine action. Jian Feng. Department of Biological Sciences, Neuroscience Program, Florida State University, Tallahassee, FL 32306, USA; Neuroscience

Department, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. TET family proteins have been shown recently to oxidize 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), which then further leads to unmethylated cytosine. This finding provides a novel mechanism of active DNA demethylation. Although 5hmC is most enriched in brain compared with other organs, the influence of 5hmC and TET on complex behavior remains unknown. Here, we first demonstrate that repeated cocaine administration decreased TET1 expression in nucleus accumbens (NAc), a key brain reward structure, in both mice and humans. Mouse behavioral assays after viral-mediated TET1 overexpression or knockdown in NAc indicated that TET1 negatively regulates behavioral responses to cocaine. Through genome-wide 5hmC capture and sequencing, we profiled cocaine-triggered global dynamics in 5hmC in NAc. Besides a robust regulation of 5hmC at putative distal enhancer regions, we identified major 5hmC changes within coding regions of specific genes. By superimposing such 5hmC changes on transcription changes determined by RNAseq, we found that repeated cocaine-triggered 5hmC alterations enrich both at genes that show steady state expression regulation after cocaine, as well as at genes poised for abnormal transcriptional induction in response to a subsequent cocaine challenge. In addition, these genes are highly clustered in neural functional groups with many known to have pivotal roles in drug addiction. Such induction of 5hmC, which occurred similarly following TET1 knockdown alone, correlated with increased expression of these genes as well as with their alternative splicing in response to cocaine administration. Interestingly, we have also found that 5hmC alterations at certain genes last up to a month after repeated cocaine exposure. Though 5hmC is known as a transient epigenetic state between methylated and unmethylated cytosine, our findings support a role of 5hmC as a stable epigenetic mark in the brain. In summary, our study reveals a novel epigenetic mechanism of cocaine action, and provides fundamental insight into how 5hmC regulates neural transcription in vivo.

Methamphetamine-Associated Memory is Regulated by a Writer and an Eraser of Permissive Histone Methylation. Courtney A. Miller. Department of Metabolism and Aging, Department of Neuroscience, The Scripps Research Institute, Florida, USA. Memories associated with drugs of abuse, such as methamphetamine (METH), increase relapse vulnerability to substance use disorder by triggering motivation to seek the drug. The nucleus accumbens (NAc) is essential to these drug-associated memories, but underlying mechanisms are poorly understood. Posttranslational chromatin modifications, such as histone methylation, modulate gene transcription, thus we investigated the role of two associated epigenetic modifiers in METH-associated memory. Conditioned place preference was used to assess the epigenetic landscape in the NAc supporting METH-associated memory. The impact of histone methylation (H3K4me2/3) on the formation and expression of METH-associated memory was determined by focal, intra-NAc knockdown (KD) of a writer, the methyltransferase MLL1, and an eraser, the histone demethylase KDM5C, of H3K4me2/3. A survey of chromatin modifications in the NAc of animals forming a METH-associated memory revealed the global induction of several modifications associated with active transcription. This correlated with a pattern of gene activation, as revealed by microarray analysis, including upregulation of Oxtr and Fos, whose promoters also had increased H3K4me3. KD of Mll1 reduced H3K4me3, Fos and Oxtr levels and disrupted METH-associated memory. KD of Kdm5c resulted in hypermethylation of H3K4 and prevented the expression of METH-associated memory. The development and expression of METH-associated memory are supported by regulation of H3K4me2/3 levels by MLL1 and KDM5C, respectively, in the NAc. These data indicate that permissive histone methylation, and the associated epigenetic writers and erasers, represent potential targets for the treatment of substance abuse relapse, a psychiatric condition perpetuated by unwanted associative memories.

Influence of genomic imprinting on metabolism and behavior. Xin-Yun Lu. University of Texas Health Science Center at San Antonio, USA. Genomic imprinting is an epigenetic phenomenon by which one allele of a specific gene is silenced according to parental origin. Noncanonical imprinting involves silencing of the maternal or paternal allele in tissue- or cell-specific manners. Growth factor receptor-binding protein 10 (Grb10) is an adaptor protein that is paternally expressed in the brain and maternally expressed in peripheral tissues. While the materal allele acts to restrict fetal growth in the periphery, the functions of the paternal-allele expression in the brain remain poorly understood. Here we show Grb10 is

abundantly expressed in the brain regions involved in the regulation of appetite and metabolism. Diet manipulations regulate Grb10 levels in the hypothalamus. Mice with a disrupted paternal allele exhibit ablation of Grb10 expression in the brain and show altered feeding behavior, circadian locomotor activity and body weight with sex differences. Knockdown of Grb10 in the adult hypothalamus decreases food intake and body weight in diet-induced obese mice. Moreover, we demonstrate mechanistic interactions between Grb10 and adiposity signals. Our results implicate a role of allele- and tissue-specific gene regulation in appetite control and obesity.

Epigenetics of Social Bonding in Prairie Voles. Mohamed Kabbaj, Zuoxin Wang, Yan Liu, Lindsay Elvir. Florida State University, USA. The prairie vole is a social monogamous rodent that forms long-lasting pair bonds, displays selective aggression, and provides sustained bi-parental care for their offspring. Our group has recently provided evidence for epigenetic regulation of partner preference formation, a form of prairie vole social attachment. In our ongoing work, we are attempting to establish, for the first time, the In utero sodium valproate (VPA) exposure in prairie voles, a model which has, in other rodent species, recapitulated various behavioral and anatomical impairments observed in autistic patients. We believe that the prairie vole model can effectively exhibit some traits of complex human social behaviors, such as social attachment, and can express analogous genetic pathways that regulate social behaviors. Our results so far show that VPA administration to pregnant prairie voles during early gestation causes an inability in their offspring to form a partner preference in the absence and presence of mating. Now that we have validated this VPA model in prairie voles, we are trying to reverse some of the social deficits observed using molecules that can alter the epigenome. This work was supported by NIMH/NIH.

10:30-11:30 **Keynote: Yasmin Hurd**, Icahn School of Medicine at Mount Sinai, USA. High Times for Cannabis: Epigenetic Imprint and its Legacy on Brain and Behavior.

High Times for Cannabis: Epigenetic Imprint and its Legacy on Brain and Behavior. Yasmin L. Hurd. Icahn School of Medicine at Mount Sinai, USA. Notwithstanding recent changes in its legalization status in many countries worldwide, marijuana (cannabis sativa) continues to be the illicit drug most used in western societies. The reduced perception regarding any risk associated with its use as well as the emergent industry evolving around 'medical marijuana' has contributed to the growing use of the drug. The fact that the increase in cannabis use is prominent in individuals of childbearing age has significant implications far extending their own lifespan. As such, our research efforts have focused on the impact of □9-tetrahydrocannabinol (THC; psychoactive component of cannabis) exposure during critical periods of development, such as during pregnancy and adolescence. Our findings to date suggest significant impact of such exposure on mesocorticolimbic neuronal systems germane to features of reward, motivation, negative affect and goal-directed behaviors in adulthood. It is clear that cannabinoid exposure alters the normal epigenetic landscape and related neurobiological systems particularly relevant to synaptic plasticity. Discussion of recent findings will also be placed in the framework of cell-specific alterations. Additionally, evidence will be discussed regarding the potential cross-generational impact of THC exposure to influence the epigenome and behavior of future generations. Altogether the studies to date emphasize a protracted neurobiological legacy of cannabis exposure.

1:30-3:30 ***Zebrafish and human brain disorders: A new tool in behavioral neuroscience.*** Chair: Robert Gerlai.

Behavioral, anatomical, and pharmacological phenotyping of zebrafish models of autism. Ellen J. Hoffman1,2, Marcus Ghosh3, Katherine J. Turner3, Steve W. Wilson3, Matthew W. State5, Antonio J. Giraldez4 , Jason Rihel3. 1Child Study Center, Yale School of Medicine, New Haven, CT 06510, USA 2Program on Neurogenetics, Yale School of Medicine, New Haven, CT 06510, USA 3Department of Cell and Developmental Biology, University College London, Gower Street, London WC1E 6BT, UK.

Department of Genetics, Yale University School of Medicine, New Haven, CT 06510, USA 5Department of Psychiatry, University of California San Francisco, San Francisco, CA 94143, USA. Autism spectrum disorders (ASD) are a group of neurodevelopmental syndromes characterized by repetitive behaviors, restricted interests, and deficits in social interaction and communication. Modern genomics approaches such as whole exome sequencing of patients are rapidly linking dozens, even hundreds, of genes to ASD, but the underlying mechanisms of the disease remains poorly understood, limiting the development of targeted treatments. Taking advantage of the optical transparency and cost-effective behavioral phenotyping of the zebrafish model, we have been examining the neurodevelopmental and behavioral changes caused by mutations in several ASD risk genes. In zebrafish ASD models, we observe alterations in the organization of specific neuronal cell populations in the larval forebrain and hypothalamus, such as a loss of GABAergic neurons in the forebrain and hypothalamus. Additionally, we see changes in seizure propensity and sleep-wake behaviors in several zebrafish ASD mutant lines, including an extreme nighttime hyperactivity in loss-of-function contactin Associated Protein-like 2 (cntnap2) mutants. By comparing the sleep-wake phenotypes of ASD mutants to behavioral changes elicited by a panel of nearly 6000 small molecules, we are able to use predictive pharmacology to identify small molecules suppressors of these ASD-associated sleep phenotypes. Several estrogenic compounds are capable of selectively altering sleep in ASD mutant zebrafish, suggesting that perturbed estrogen signaling in discrete sleep circuits may underlie these behavioral observations. The presentation will discuss on-going efforts to visualize sleep circuit activity and to map small molecule interventions onto specific neuronal targets in our zebrafish ASD models.

Screening of natural products using zebrafish behavior. Ortiz, José G., del Valle-Mojica, L., Rosa-Falero, Coral and Torres-Hernández, Bianca. Department of Pharmacology and Toxicology, University of Puerto Rico School of medicine, San Juan, Puerto Rico. Natural products are a possible source of new drugs. However, identification of drug candidates requires screening overwhelming amounts of compounds. Zebrafish are ideally suited for target and phenotypic screening. We screen adult zebrafish for anticonvulsant activity using pentylenetetrazole-induced seizures (PTZ). Anxiolytic activity is also tested in groups of zebrafish (as opposed to individuals) using light/dark preference. Zebrafish embryos have also been used, although their limited behavioral repertoire hinders their use in phenotypic screening. Valeriana officinalis extracts have anxiolytic effects that are mediated (in part) by mGluR I and II receptors, while its anticonvulsant effects involve by GABAa, A1, A2, and Glu receptors (except KA). Citrus aurantium (CA) from Puerto Rican folklore, also has anticonvulsant properties that are mediated by mGluR I and II but not GABAa receptors. CA also has anxiolytic properties, but the receptors involved have not been identified. Kratom (Mitragyna speciosa), often found in synthetic cannabinoid preparations has proconvulsant effects, without significant effects on anxiety. These results exemplify the potential of zebrafish in screening complex mixtures such as those found in natural products preparations.

What makes us social? Analysis of a zebrafish model. Soaleha Shams. Cell & Systems Biology Dept, Univ. of Toronto Mississauga, Mississauga, ON, Canada. The zebrafish has been a favorite of developmental biologists and geneticists for decades and as of recent, it is becoming popular among behavior researchers. While transparent eggs and semi-transparent embryos made zebrafish useful for studying early development and organogenesis, high level of homology with human nucleotide sequence and functionally relevant domains of proteins, and availability of sophisticated forward and reverse genetic techniques made it convenient to manipulate the zebrafish genome. Compared to other model species, behavioral studies using zebrafish, especially exploration of social behavior, are relatively new. Social interaction is an important and complex aspect of zebrafish behavior, but one which can be quantified with relative ease and simplicity. This symposium highlights studies that have successfully induced and measured social behavior employing various methods of observation using single zebrafish or groups of zebrafish. Effect of pharmaceutical treatments including, environmental toxins, common and controlled substances and drugs of abuse, on zebrafish social interaction are also presented. Moreover, non-pharmaceutical manipulations, biotic and abiotic factors that alter, enhance, or impair social behavior are also discussed. Finally, findings from zebrafish studies are compared and contrasted with other social

animals. This analysis helps establish translationally relevant zebrafish research as a tool to simplify, explore, and understand human social behavior and disorders involving social abnormalities.

Zebrafish and alcohol: A simple vertebrate for a complex disease problem. Robert Gerlai University of Toronto Mississauga. The zebrafish has been in the forefront of genetics and developmental biology for over four decades but more recently its utility in behavioral neuroscience has started to be recognized too. For example, it has been proposed to be a useful research tool for the analysis of the effects of alcohol on the vertebrate brain and for the modeling of complex alcohol related human disorders. The current talk will present experimental examples showing the utility of the zebrafish in the analysis of acute and chronic alcohol effects on brain function and behavior. It will also briefly discuss a zebrafish fetal alcohol spectrum disorder model. For example, results of psychopharmacological analyses revealed important contribution of specific dopamine receptors mediating acute alcohol effects. DNA microarray analyses showed significant alteration of mRNA expression from almost 2000 genes after chronic alcohol exposure in zebrafish and revealed a large family of genes encoding the solute carrier family proteins to be significantly overexpressed. Embryonic alcohol exposure has been found to lead to significant changes in social stimulus induced activation of the dopaminergic system. Importantly, many of these neurobiological changes have been found to be accompanied by significant behavioral alterations encompassing changes in motor responses, fear responses, and social behavioral responses. The results obtained so far with zebrafish suggest good face validity (similar appearance of effects) as well as construct validity (similar mechanisms) underlying alcohol effects in zebrafish. Given the simplicity, ease and low cost of maintenance, high fecundity of the zebrafish, the sophistication of genetic tools developed for this species, and the ease and precision with which alcohol can be administered to zebrafish, the above results suggest that this species will be an excellent translational tool with which alcohol related human disorders may be modeled and their mechanisms analyzed.

1:30-3:30 ***Early life stress and serotonin: Effects on social and emotional health.*** Chair: Jodi Pawluski.

Prenatal exposure to SSRI antidepressants and lessons we can learn about child development. Tim F. Oberlander, MD, FRCPC, Dept of Pediatrics, Child and Family Research Institute, University of British Columbia, Vancouver, Canada. Selective serotonin reuptake inhibitor (SSRI) antidepressants are the most common antidepressant treatment used during pregnancy and the postpartum period. Up to 10% of pregnant women are prescribed SSRIs. SSRIs inhibit the reuptake of a key neurodevelopmental signal, serotonin (5HT), thereby increasing central 5HT levels during developmentally sensitive periods. Given serotonin's key role in early brain development, SSRI use in pregnancy raises critical and unanswered questions about the long term developmental effects associated with early changes in brain 5HT levels. Recent attention has focused on increased risks for disordered or delayed development associated with prenatal exposure to SSRIs, such as ADHD, mood and autism spectrum disorder (ASD). This presentation will explore key evidence showing that prenatal SSRI exposure potentially shapes child development - for better and for worse. These findings will be presented as a way to illustrate how developmental outcomes in this context might offer a broader perspective illustrating risks and potential benefits associated with SSRI use during pregnancy and what lessons we can learn about child development in general.

Effects of differential maternal care on sibling differences in anxiety, mothering, and serotonin mechanisms in rats. Christina M. Ragan. Colgate University. Maternal care during early postnatal life is well known to have tremendous influences on offspring neurobiological and socioemotional development. Many studies have examined the effects of differential maternal care received on offspring phenotype in rodents between litters, but the consequences of differential mothering within litters on individual offspring neurobehavioral development are rarely examined. To fill this gap in the literature, my research focuses on how variability in maternal care received (measured by maternal licking of pups) among rat siblings relates to the siblings' emotional and maternal behaviors and neurobiological changes later in life. As previously reported, there is indeed within-litter variability in maternal care received as

some pups receive up to three times more maternal licking bouts compared to their siblings. Surprisingly, the number of maternal licking bouts that females received positively correlates with their later fear and anxiety-related behaviors in adulthood. In addition, maternal care received is also positively correlated with female offspring maternal responsiveness. I have also found that medial prefrontal cortex expression of tryptophan hydroxylase-2 (TPH2; enzyme necessary for serotonin synthesis) is negatively associated with early maternal licking received. Notably, this cortical TPH2 has opposite associations with maternal responsiveness of sensitized virgins compared to postpartum females. To follow up with my previous work, I am currently investigating how manipulation of early serotonin circuitry in pups exposed to acute clomipramine (a non-selective serotonin reuptake inhibitor) vs. saline during postnatal days 4-10 can influence pup-mother interactions and offspring behavioral and physiological responses to anxiety-provoking environments later in life. These results indicate that long-term effects of differential maternal care received among siblings, while often overlooked, may contribute to within-litter differences in socioemotional behaviors and their related neurobiological correlates later in life and is an important area to investigate further. Research support: Ruth L. Kirschstein National Research Service Award (NRSA) National Institute of Child Health and Human Development. 2013-2015. Training Grant Number: 1 F32 HD075758-01A1 and internal funds from the Pennsylvania State University and Colgate University.

Developmental epigenetic programming in serotonin-transporter deficient mice. Daniel L.A. van den Hove1,2. 1Maastricht University, School for Mental Health and Neuroscience (MHENS), Department of Psychiatry and Neuropsychology, P.O. Box 616, 6200 MD Maastricht, the Netherlands. 2University of Wuerzburg, Laboratory of Translational Neuroscience, Department of Psychiatry, Psychosomatics and Psychotherapy, Fuechsleinstrasse 15, 97080 Wuerzburg, Germany. The serotonin transporter gene (5-HTT/SLC6A4)-linked polymorphic region has been suggested to have a modulatory role in mediating effects of early-life stress exposure on psychopathology rendering carriers of the low-expression short (s)-variant more vulnerable to environmental adversity in later life. The underlying molecular mechanisms of this gene-by-environment interaction are not well understood, but epigenetic regulation including differential DNA methylation has been postulated to have a critical role. Recently, we used a maternal restraint stress paradigm of prenatal stress (PS) in 5-HTT-deficient mice and showed that the effects on behavior and gene expression were particularly marked in the hippocampus of female 5-Htt+/− offspring. Here, we examined to which extent these effects are mediated by differential methylation of DNA. For this purpose, we performed a genome-wide hippocampal DNA methylation screening using methylated-DNA immunoprecipitation (MeDIP) on Affymetrix GeneChip Mouse Promoter 1.0 R arrays. Using hippocampal DNA from the same mice as assessed before enabled us to correlate gene-specific DNA methylation, mRNA expression and behavior. We found that 5-Htt genotype, PS and their interaction differentially affected the DNA methylation signature of numerous genes, a subset of which showed overlap with the expression profiles of the corresponding transcripts. For example, a differentially methylated region in the gene encoding myelin basic protein (Mbp) was associated with its expression in a 5-Htt-, PS- and 5-Htt × PS-dependent manner. Subsequent fine-mapping of this Mbp locus linked the methylation status of two specific CpG sites to Mbp expression and anxiety-related behavior. In conclusion, hippocampal DNA methylation patterns and expression profiles of female prenatally stressed 5-Htt+/− mice suggest that distinct molecular mechanisms, some of which are promoter methylation-dependent, contribute to the behavioral effects of the 5-Htt genotype, PS exposure and their interaction. Interestingly, blood MBP methylation was shown to be reliable epigenetic signature in human psychopathology, as assessed in three independent human cohorts on prenatal stress, post-traumatic stress disorder (PTSD) and panic disorder (PD).

Consequences of venlafaxine treatment and/or maternal adversity on neurobehavioral development of rat offspring. Császár Eszter1,2, Melicherčíková Kristína1,2, Mach Mojmír1, Ujházy Eduard1, Dubovický Michal1. 1Institute of Experimental Pharmacology and Toxicology, Slovak Academy of Sciences, Department of Developmental and Behavioral Toxicology, Bratislava, Slovak Republic; 2Department of Pharmacology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovak Republic. The major dilemma for gynecologists is to treat or not to treat depression during gestation and lactation. Consequences of untreated depression can be so serious that the benefit of antidepressant

therapy may overweigh the possible risk for injury of fetal/neonatal development. Currently up to 10% of women are treated with antidepressants during pregnancy and lactation. Venlafaxine, a representative of serotonin and noradrenaline reuptake inhibitors, is used to treat a wide spectrum of mood disorders. However, there is only a limited number of studies which evaluated consequences of venlafaxine therapy during pregnancy and lactation. Recently, our effort is focused on the study of consequences of venlafaxine treatment and/or maternal adversity during the pre- and early postnatal period on selected neurobehavioral variables of the rat offspring. The results of our investigations showed that administration of venlafaxine alone did not affect basic reproductive variables and biochemical profile of juvenile rat offspring. Other study demonstrated that adult male and female offspring treated via mothers with venlafaxine alone exhibited less “anxious” and “depressive” behaviors in a new environment. Studies concerned with consequences of venlafaxine treatment combined with maternal adversity did not reveal any alterations in juvenile play behavior in familiar home cage environment. However, juvenile and adolescent rats of both sexes exposed to an open field showed an increased anxiety-like behavior. Based on the results obtained, we suggest that pre- and early postnatal exposure to venlafaxine and/or maternal adversity may interfere with functional brain development and can cause subtle behavioral alterations in the offspring. These changes may not occur immediately or shortly after the birth but later in juvenile and adolescent age or even in adulthood. The studies were supported by the grants VEGA 2/0129/15 and 2/0168/15.

3:30-4:30 **Travel Award Blitz.**

A novel oxytocin-like compound reduces motivation to self-administer methamphetamine and relapse to methamphetamine seeking in rats. SarahBaracz1,2, NicholasEverett1, MichaelBowen2, MichaelKassiou2, JenniferCornish1, IainMcGregor2. 1Macquarie University, NSW, Australia 2 University of Sydney, NSW, Australia. The psychostimulant methamphetamine (METH) is an addictive illicit drug. The neuropeptide oxytocin has been shown to robustly reduce METH-related reward and abuse in rodents. However, its poor permeability of the blood brain barrier and limited oral bioavailability impacts on its therapeutic potential. The recent development of synthetic oxytocin-like compound -1 (SOC-1), a small molecule with enhanced blood brain barrier penetration and oral bioavailability with oxytocin-like effects on enhancing social behaviours, is a promising therapeutic alternative. The ability of SOC-1 to reduce METH abuse and relapse, although, had not yet been investigated. The aim of the study was to investigate whether SOC-1 administration reduces motivation for METH intake and drug-primed reinstatement to METH-seeking behaviour. Male Sprague Dawley rats with implanted jugular vein catheters were initially trained to self-administer METH (0.1 mg/kg/infusion) under a fixed ratio 1 schedule of reinforcement. Rats then advanced to a progressive ratio (PR) reinforcement schedule to examine the effect of SOC-1 (0, 1.25, 2.5, 5, and 10 mg/kg) intraperitoneal (ip) administration on motivation for METH taking, or underwent testing of SOC-1 (0, 2.5, 5, and 10 mg/kg; ip) effects on drug-primed reinstatement of METH seeking following extinction. Our results showed that SOC-1 administration reduced PR responding for METH (5mg/kg and 10mg/kg doses) and relapse to METH-seeking behaviour (all tested doses). Overall, these findings demonstrate that SOC-1 has similar effects to oxytocin on reducing methamphetamine-taking and -seeking behaviours and provides further support for its application as a therapeutic tool. This work was supported by an NHMRC grant 1088711.

The subunit-specific role of NMDA receptors in behavioral dysfunctions evoked by traumatic event. Laszlo Biro1,2, Eva Mikics1, Eszter Sipos1, Christina Miskolczi1, Mate Toth1, Jozsef Haller1. 1Laboratory of Behavioural and Stress Studies, Department of Behavioural Neurobiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary; 2Janos Szentagothai Doctoral School of Neurosciences, Semmelweis University, Budapest, Hungary. Traumatic life events often lead to the development of post-traumatic stress disorder (PTSD), a highly debilitating psychiatric condition with long-lasting symptomatology. Recent reports suggest that glutamatergic receptor function in limbic regions, particularly N-methyl-D-aspartate receptors (NMDAR) containing different subunits play an important role in the development of trauma evoked behavioral dysfunction. Here we investigated the effects of the general NMDA blocker MK-801 and specific NR2A, NR2B and NR2C/D subunit antagonists

on the expression of conditioned fear, a frequently used model of PTSD. Rats were exposed to a single series of 3mA footshocks and were tested 1 or 28 days later to compare acute and long-lasting effects of trauma on behavior and target gene expression levels in brain areas relevant for PTSD. When re-exposed to the traumatic context, rats showed a dramatic increase in freezing behaviour (conditioned fear) compared to unshocked controls. We found that the NR2A antagonist PEAQX and NR2C/D antagonist PPDA did not affect conditioned fear responses 1 or 28 days after traumatic shock exposure. However, both MK-801 and the selective NR2B subtype antagonist Ro25-6981 significantly reduced the duration of freezing in the conditioned fear test at both time points. To uncover acute and long-lasting effects of trauma on NMDA receptor gene expression in brain areas relevant in PTSD, we performed quantititve real-time PCR measurements on tissue punches from dorsal hippocampus, medial prefrontal cortex, basolateral and central amygdala. We found that NR2A and NR2B subunit mRNA expression was increased in the medial prefrontal cortex, on the first day after the traumatic event, while only NR2B mRNA levels remained elevated 28 days after shock exposure. Both NR2A mRNA expression in the basolateral amygdala and NR2B mRNA expression in the dorsal hippocampus temporarily increased 1 day after shock exposure. According our preliminary data mRNA expression levels of the key epigenetic enzyme DNMT3a was elevated 1 day after trauma exposure in basolateral amygdala, but this effect disappeared 28 days later. Our results suggest that studying the role of glutamate neurotransmission in a subunit-selective manner opens novel opportunities for understanding the mechanisms underlying trauma-induced behavioral dysfunctions. Our findings may contribute to a better understanding of the pathomechanisms of PTSD.

Examining the effect of chronic intranasal oxytocin administration on the neuroanatomy and behaviour in two different autism-related mouse models. Buchwald, Zsuzsa[1]; Stuive, Monique[1]; Ellegood, Jacob[1]; Anagnostou, Evdokia[2]; Lerch, Jason[1]. [1]Mouse Imaging Center, Hospital for Sick Children, Toronto, Canada, [2]Holland Bloorview Kids Rehabilitation Center. Introduction: Autism is a neurodevelopmental disorder characterized by social communication deficits and repetitive behaviors. Oxytocin is known for its ability to promote social behaviours and may be a promising therapeutic for autism. To determine what might contribute to response susceptibility, we treated the 16p11.2 deficiency and FMR1 knockout mouse models with intranasal oxytocin. Methods: Intranasal oxytocin was administered once a day, for 28 days, starting at 5 weeks of age. During the third week of treatment, the behaviour of the mice was assessed in multiple domains, including sociability and repetitive behaviours. The mice underwent in vivo and ex vivo neuroimaging throughout various points in the study. Results: Treatment had no significant effect on neuroanatomy and, for the most part, did not enhance the behaviours of either mouse model, though it slightly increased social behaviours in the 16p11.2 mouse. Discussion: Neither model showed a treatment effect in their neuroanatomy, and very little effect on behaviour. This indicates that oxytocin may not be a good treatment option for either the 16p11.2 or FMR1 mutant mice, and therefore humans with the 16p11.2 mutation and children with Fragile X Syndrome. Future directions involve looking at the response of multiple strains of autism-related mouse models to several promising therapeutics used in human patients with autism, yielding the ability to establish a translational paradigm for predicting responders from non-

Temporal dissociation of activity-dependent alterations in prefrontal BDNF expression during decision-making shifts. Robert D. Cole1, Vinay Parikh1. 1Department of Psychology and Neuroscience Program, Temple University, Philadelphia, PA, USA. Brain-derived neurotrophic factor (BDNF) is essential for regulating learning, memory and motivational processes. Evidence suggests that BDNF infusion into the dorsal striatum regulates cognitive flexibility. However, the role of endogenous BDNF signaling in flexible decision-making remains unknown. Activity-dependent alterations in BDNF expression is a key event in synaptic plasticity and cognition. As frontostriatal circuits involving discrete regions of the prefrontal cortex (PFC) and striatum are critical in maintaining different forms of cognitive flexibility, such as strategy shifting (SS) and reversal learning (RL), we hypothesized that shifting to new strategies would produce neuronal activity-dependent alterations in BDNF expression in these circuits. Mice were trained in an operant task requiring the animals to either shift a visual cue-based strategy to an egocentric spatial response-based strategy or to flexibly adapt to a reversal of initial response

contingencies. Brains were removed either during the initial learning or after complete acquisition of the new strategy. Quantitative immunohistochemical examined BDNF and cfos expression in the regions of interest. BDNF expression in striatal synaptosomes was examined using immunoblotting. BDNF-positive cell counts increased in the orbito-PFC (oPFC) and medial-PFC (mPFC) following strategy and reversal shifts ($p<.01$). A significant time x behavioral shift interaction was observed ($p<0.01$). During the early phase, an overall increase in BDNF positive cells was noted in all regions irrespective of the shift type. Synaptic BDNF levels also increased in the striatum ($p<.05$) indicating overflow of PFC BDNF to target striatal regions. However, BDNF effects were dissociated based on the shift type following task acquisition. RL was mostly associated with higher BDNF in the oPFC while mPFC prefrontal regions exhibited elevated BDNF expression during SS. Moreover, performance-related increases in BDNF/c-fos co-labeling in the oPFC and mPFC regions were revealed ($p<.01$). Flexible decision-making produces temporal alterations in the frontostriatal BDNF expression. Moreover, the dissociation between cortical region-specific neuronal activity and BDNF levels based on higher-order and lower-order behavioral shift becomes apparent only after the strategy for optimal performance is acquired. As BDNF regulates synaptic transmission, prefrontal BDNF alterations may play a critical role in modulating corticostriatal activity to maintain shifts in strategies with changing environmental demands. Deficits in frontoexecutive processes like cognitive flexibility are associated with major neuropsychiatric disorders such as schizophrenia, addiction and depression. Therefore, BDNF may serve as a neurobiological substrate for a neurocognitive endophenotype common to multiple psychiatric conditions.

A gene x environment mouse model of switching between affective states: Reducing DAT function results in hypersensitivity to seasonal photoperiod-induced changes in affect. Zackary A. Cope, Davide Dulcis, Jared W. Young. University of California San Diego, Department of Psychiatry, USA. Bipolar disorder (BD) is a debilitating mental illness characterized by chronic relapse and switching between extreme moods. Left untreated, affected individuals experience switches between depressed mood (sadness, anhedonia, amotivation, suicidal thoughts), and mania (euphoria, impulsivity, risky behavior, reward seeking). While mechanisms underlying unipolar symptoms are relatively well understood, mechanisms underlying switches between the two extremes remain unknown. The key to understanding BD relies on identifying mechanism(s) driving switches between these two extremes in behavior within the same subject. Neurotransmitter switching between somatostatin (SST) and the dopamine synthesizing enzyme tyrosine hydroxylase (TH) has been observed in a population of rodent paraventricular hypothalamic (PaVH) neurons. This switch resulted from exposure to short-active (SA, 19 hrs light:5 hrs dark) and long active (LA, 5 hrs light:19 hrs dark) photoperiods respectively. Each condition was associated with one of two dichotomous behavioral profiles. Specifically, LA photoperiod increased TH expression in PaVH cells, inducing maniarelevant behavior, while SA photoperiod increased SST expression in these same cells resulting in elevated CRF levels and depression-relevant behavior (Dulcis, et al. Science, 2013). This observation is noteworthy because seasonal variations in day-length have been linked to relapse vulnerability in BD patients (Berk, et al. Acta Psychiatr Scand. 2007). Further, a 40% reduction in dopamine transporter (DAT) expression has been measured in euthymic BD patients (Anand, et al. Bipolar Disorders, 2011), which may represent a mechanism by which seasonal variations in day-length induce extremes in affect. Here, we exposed mice with an ~50% reduction in DAT expression (DAT-HY) to SA or LA photoperiods to assess the degree to which these manipulations can induce dichotomous behavior. Increased depression-relevant forced-swim immobility was observed in mice housed under SA conditions ($F(2,64),=4.3$, $p<0.05$), while LA photoperiod was resulted in increased mania-relevant open arm exploration ($F(2,61)=4.7$, $p<0.05$). These effects were exaggerated in DAT HY mice, consistent with preliminary findings. DAT-HY mice also exhibited hyperactivity across multiple dependant measures in the behavioral pattern monitor, regardless of photoperiod state. Further, we performed a multi-dimensional behavioral characterization in these same mice following exposure to altered photoperiods including cross-species relevant measures of feedback related decision making, reward learning, effortful motivation, and sensory processing. These results, the extent to which they recapitulate a BD relevant profile in each illness phase, associated immunohistochemical switching, and

how they relate to treatment development, will be fully discussed. This study was funded by NIH R01 MH104344.

Loss of neuronal activity in the central amygdala of seizure prone Fmr1 KO mice is conserved across multiple mouse lines susceptible to audiogenic seizures. Davenport MH1,2; Robinson CK1,2; Grainger LM1; King AJ1,2; Erickson CA1,2; Schaefer TL1. 1Department of Psychiatry, Cincinnati Children's Hospital Medical Center, Cincinnati OH USA; 2University of Cincinnati, Cincinnati OH USA. Fragile X Syndrome (FXS) is the most prevalent, known, single gene cause of autism and heritable intellectual disability. FXS is caused by an expanded CGG repeat in the 5' UTR of the Fragile X Mental Retardation 1 (FMR1) gene that results in its transcriptional silencing leading to neuronal hyperexcitability. Individuals with FXS experience a wide range of behavioral, intellectual, and physical abnormalities including anxiety, hypersensitivity to sensory stimuli, and an increased risk of seizures. These phenotypes are well conserved in the Fmr1 KO mouse model of FXS. Appropriate extracellular signal-regulated kinase 1/2 activity (ERK) is critical for activity dependent synaptic plasticity and appropriate behavior. ERK activation is typically associated with neuronal activity in both excitatory and inhibitory neurons. Under basal, non-challenged conditions we have shown that ERK activation is elevated in the amygdala, hippocampus and striatum of mice and in blood lymphocytes of mice and humans with FXS independent of changes in ERK total protein levels. Since it is clear that activity dependent neuronal signaling is altered in FXS, we hypothesized that ERK activation is not only altered at basal conditions but also during periods of high neuronal activity and that this dysregulation is region specific. We utilized a robust audiogenic seizure paradigm that consists of a 1 min habituation, then a 2 min 120dB priming tone, followed by 1 min of silence, and finally a second 120dB tone that induces wild running and tonic/clonic seizure behavior in ~60% of Fmr1 KO mice. When examining ERK activity immediately after AGS, we discovered a striking inactivation of ERK in the central nucleus of the amygdala (CeA), the major inhibitory output of the basal ganglia, only in mice that experience seizure. In contrast, the lateral amygdala (LA), which serves as the primary input center of the amygdala and consists of mostly excitatory neurons, becomes over activated in these same seizure mice. Based upon preliminary in situ hybridization data for the immediate early gene c-Fos we also demonstrated that these ERK effects during seizure are concomitant with elevated neuronal firing in the LA and reduced neuronal firing from the CeA in Fmr1 KO mice that seized. Further study demonstrated that the deactivation of the CeA begins during the priming phase of AGS, preceding the initiation of seizure behavior. ERK activation patterns across seizure resistant and seizure prone mice including B6 WT littermates, Fmr1 KOs, maternal Ube3a KOs (Angelman Syndrome model), and outbred CD1 mice (which are susceptible to AGS) further suggest that decoupling of neuronal activity between the lateral and central amygdalar nuclei is a key event in AGS susceptibility across genetic mutants and backgrounds. Future studies will determine if similar decoupling contributes to other amygdala dependent behavioral dysfunctions in FXS.

CRHR1 Mediation of neuroplasticity and neuroinflammation in the hippocampus following global cerebral ischemia. Patricia Barra de la Tremblaye1, PhD and Hélène Plamondon1, PhD. 1 Behavioural Neuroscience Group, Department of Psychology, University of Ottawa . Ischemic brain injury triggers restorative processes characterized by rapid neuronal growth and neuroplasticity, critical to optimize functional recovery of individuals post stroke. Brain-derived neurotrophic factor (BDNF) may be a promising avenue in the treatment of cerebral ischemic injury because this neurotrophin can enhance structural plasticity and cognitive performance. Mechanisms controlling release of BDNF are mediated by corticotrophin-releasing hormone (CRH) acting through its CRH type1 receptor in stressful conditions. However, whether CRH can mediate the release of BDNF in the reparative process triggered by ischemic injury remains to be characterized. Recently, we demonstrated that Antalarmin (ANT), a selective CRHR1 antagonist, can block the persistent neuroendocrine dysfunctions observed following global cerebral ischemia. In the study to be presented, we investigated the effect of ANT on the levels of BDNF and other plasticity markers, as well as on functional recovery after cerebral ischemia. Specifically, Male Wistar rats (N = 50) were subjected to sham surgery or global cerebral ischemia using the four vessel occlusion (4VO) model. ICV injection of ANT (2µg/2µl) or vehicle was administered 30 min prior to ischemia. Behavioural testing was initiated 7 days post ischemia and included assessment of anxiety and locomotor

behavior in the elevated plus maze and open field, and fear and spatial learning in a Y-maze passive avoidance task and in the Barnes maze, respectively. Immunofluorescence served to detect BDNF and TrkB expression in the hippocampus, basal lateral amygdala (BLA), and the paraventricular nucleus of the hypothalamus (PVN) 30 days post reperfusion, and expression of markers association with neuronal injury and inflammation, including NeuN, glial fibrillary acidic protein (GFAP), ionized calcium binding adaptor (IBA1) and tumor necrosis factor α (TNFα). The data revealed improved spatial memory and fear retention in ANT-treated ischemic rats ($p < 0.01$). ANT also attenuated ischemia-induced increased and decreased BDNF and TrkB mRNA and protein levels in the amygdala and hippocampus, respectively ($p < 0.05$). The prolonged heightened BDNF and TrKB expression at the PVN also appeared influenced by CRHR1 signaling. ANT blunted post-ischemic IBA1, GFAP and TNFα-immunoreactivity in all hippocampal sub-regions and conferred neuronal protection in the CA1 and BLA ($p < 0.05$). Together, these findings suggest that CRHR1 activation upon cardiovascular insults significantly contributes to ensuing neuronal and functional changes influencing post ischemic recovery. This work was supported by a grant from the National Science and Engineering Research Council of Canada to Dr. Hélène Plamondon and internal funding from the University of Ottawa.

Prodynorphin genetic polymorphisms and ventral striatonigral pathway activity contribute to individual differences in novelty seeking and positive reward traits. Gabor Egervari1,2, Didier Jutras-Aswad1, Joseph Landry1,2, Michael L Miller1,2, Sarah Ann Anderson1,2, Michael Michaelides1,2, Michelle M Jacobs1,2, Cyril Peter1,2, Georgia Yiannoulos1, Xun Liu1, Yasmin L Hurd1,2. 1 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029, USA. 2 Department of Neuroscience, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029, USA. Genetic factors impact behavioral traits relevant to numerous psychiatric disorders and risk-taking behaviors, and different lines of evidence have indicated that discrete neurobiological systems contribute to such individual differences. This presentation will explore the relationship of genetic variants associated with neural circuits implicated in reward and novelty-seeking traits. Specifically, we focus on the prodynorphin (PDYN) gene that is enriched in the ventral striatonigral/striatomesencephalic pathway, a key neuronal circuit implicated in positive 'Go' behavioral choice and action. Our multidisciplinary approach identified a single nucleotide polymorphism (SNP), rs2235749 that modifies striatal PDYN expression through altering the binding of miR-365, a microRNA that targets the PDYN 3'-untranslated region. The SNP is significantly associated with PDYN mRNA expression particularly in the nucleus accumbens shell (NAcSh) as well as to novelty- and reward-related behavioral traits in humans and translational animal models. We provide evidence that the Pdyn-miR365 interaction in the NAcSh directly influences novelty seeking exploratory behavior and facilitates the self-administration of natural rewards. Overall, this translational study suggests that genetically determined miR-365-mediated epigenetic regulation of PDYN expression in mesolimbic striatonigral/striatomesencephalic circuits contributes to novelty seeking and positive reinforcement traits. The findings will be discussed in relation to individual vulnerability to addiction and related disorders. This work was funded by NIH DA15446.

CB1 receptor antagonism increases anxiety-like behavioural responses and alters neurochemical levels in two distinct populations of zebrafish. Amanda Facciol1, Steven Tran2, Diptendu Chatterjee1, & Robert Gerlai1,2. 1University of Toronto Mississauga, Department of Psychology. 2University of Toronto, Department of Cell & Systems Biology. The function of the cannabinoid receptor type 1 (CB1-R) is poorly understood in zebrafish and numerous inconsistent findings have been reported in the literature. In the current study, we investigate the effect of CB1-R antagonism on anxiety-like behavioral responses, dopaminergic, and serotonergic responses in two distinct populations (AB and SF) of zebrafish. AB and SF zebrafish were treated with different concentrations of AM251 (0, 0.1, 1 mg/L), the CB1-R antagonist, and behavioral responses were quantified under two different contexts; following habituation and subsequently in a novel environment. The levels of dopamine, serotonin, and their metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA) were quantified from brain tissue using high precision liquid chromatography (HPLC). We found that a 60 minute exposure to AM251 (0, 0.1, 1 mg/L) did not alter behavioral performance following habituation in

both populations. However, when subsequently transferred to a novel environment, zebrafish that were pre-treated with the highest dose of AM251 (1mg/L) exhibited increased anxiety-like behavioral responses including erratic movement, freezing, and bottom dwelling. Neurochemical analysis revealed that exposure to the highest dose of AM251 (1 mg/L) for 60 minutes increased whole-brain serotonin levels, independently of the type of population used. In contrast, exposure to 0.1 mg/L AM251 for 60 minutes decreased, whereas 1 mg/L AM251 increased whole-brain tissue levels of dopamine, DOPAC, 5-HIAA, independent of population. Our results reveal that blockade of CB1-Rs increases anxiety-like behavioral responses which is correlated with elevated whole-brain serotonin levels. In summary, our findings suggest that previous inconsistent findings regarding pharmacological blockade of CB1-Rs in zebrafish may be due to a combination of concentration and context-dependent effects. Funding: The research was funded by an NSERC Discovery Grant issued to Robert Gerlai.

SERT on speed: Enhanced emission of amphetamine-induced 50-kHz ultrasonic vocalizations in rats lacking the serotonin transporter due to long-term adaptations in 5-HT2C receptor functioning. Kisko TM1, Willadsen M1, Vörckel KJ1, Seffer D1, Schwarting RKW1, Homberg J2, Wöhr M1. 1 Behavioral Neuroscience, Experimental and Biological Psychology, Philipps-University of Marburg, Gutenbergstr. 18, 35032 Marburg, Germany; 2 Behavioral Neurogenetics, Radboud University Medical Center, Stichting Katholieke Universiteit, Geert Grooteplein 21, 6525 EZ Nijmegen, The Netherlands. Rats emit calls in the ultrasonic range, so called ultrasonic vocalizations (USV). In appetitive situations, such as social play in juveniles or mating in adults, high-frequency 50-kHz USV occur. Notably, high-frequency 50-kHz USV are also seen in response to drugs of abuse, such as amphetamine (AMPH), and it is widely believed that in rats 50-kHz USV reflect a positive affective state, possibly associated with drug wanting and/or liking. We recently demonstrated that the neurotransmitter serotonin (5-HT) is strongly involved in the modulation of appetitive 50-kHz USV in response to AMPH. Specifically, we showed that 50-kHz USV emission can be completely blocked through the administration of the 5-HT2C receptor agonist CP809,101, while the 5-HT2C receptor antagonist SB242084 results in an enhancement in 50-kHz USV production, suggesting the 5-HT2C receptor as a pharmacological target for addictive disorders. Here, we show that rats lacking the serotonin transporter (SERT) emit more appetitive 50-kHz USV in response to systemic AMPH than heterozygous and wildtype littermate controls. AMPH-induced hyperactivity did not differ between genotypes. Moreover, deficits in pre-pulse inhibition following AMPH administration were seen irrespective of genotype. Thus, the effects of AMPH on sensorimotor functions appear not to be affected by the lack of SERT. This indicates that SERT is specifically involved in modulating the rewarding aspects of AMPH, with AMPH being more rewarding in SERT knockout rats. Importantly, the increase in appetitive 50-kHz USV is likely due to long-term changes in the 5-HT system, since 50-kHz USV emission following AMPH was not enhanced in wildtype controls when the selective 5-HT reuptake inhibitor escitalopram was co-administered. To identify relevant long-term changes in the 5-HT system, we targeted the 5-HT2C receptor and found that AMPH-induced behavioral alterations were not inhibited by the agonist CP809,101 in SERT knockout rats, while a clear inhibition was seen in heterozygous and wildtype littermate controls. In support of the specificity of the involvement of the 5-HT2C receptor, we further showed that the behavioral alterations induced by AMPH were potentiated by the antagonist SB242084 in controls but not in SERT knockout rats. Together, our findings indicate that SERT knockout rats display an enhanced emission of amphetamine-induced 50-kHz ultrasonic vocalizations due to long-term adaptations in 5-HT2C receptor functioning.

Sex differences in the effects of naltrexone on appetitive and consummatory responses to ethanol in adult rats. Steven J. Nieto1, Kevin J. Winoske1, & Therese A. Kosten1. 1Department of Psychology, University of Houston, Houston, TX, United States. A wealth of animal studies provide support for the use of the mu-opioid antagonist, naltrexone, for the treatment of alcohol use disorders (AUDs). Although clinical studies show efficacy of naltrexone for AUDs, the data on whether it is differentially effective in males and females is mixed. Moreover, there are sex and gender differences in mu-opioid system that suggest naltrexone may alter alcohol self-administration differentially by sex in animals. The present study tested whether sex differences exist in the ability of naltrexone to decrease consummatory (e.g., numbers of reinforcers delivered) and appetitive behaviors (e.g., head entries into the dipper area) in an

operant alcohol self-administration paradigm. Separate groups of male and female Sprague Dawley rats (n's=611) were trained to lever press for either ethanol (10%; EtOH) or sucrose (3%; SUC) in standard operant chambers under a fixed ratio 2 (FR2) schedule of reinforcement. The effects of a broad range of naltrexone doses (0, 0.1, 0.3, 1, 3, & 10 mg/kg) were assessed in tests conducted under a progressive ratio schedule of reinforcement. In males, naltrexone administration led to dose related decreases in both appetitive and consummatory behaviors in the EtOH group, but not in the SUC group. Naltrexone was more efficacious for appetitive vs. consummatory behaviors. For example, numbers of active lever presses were significantly decreased at doses of 1 mg/kg and higher whereas consummatory behaviors were significantly reduced only at the 10 mg/kg in the EtOH group. Naltrexone administration did not significantly alter these behaviors in the female EtOH or SUC group. Together, our findings suggest that naltrexone decreases appetitive and consummatory behaviors for alcohol only in male rodents. These findings highlight the need for further investigations assessing the effectiveness of pharmacological treatments for alcohol use disorders in both genders. This work was supported by NIAAA U01AA013476.

Role for hypothalamic projections to habenula in obesity. Richard M. O'Connor and Paul J. Kenny. Department of Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, New York, NY, U.S.A. Rates of obesity are on the rise worldwide, resulting in a growing threat to public health1. Pharmacotherapies that safely reduce body weight in obesity remain elusive, partially due to our incomplete knowledge of neural mechanisms that control the feeding behaviors that drive obesity. The lateral hypothalamus (LH) plays a critical role in energy homeostasis. Indeed, electrical stimulation of LH induces feeding in satiated rodents while LH lesions result in voluntary starvation2. The LH plays a key role in regulating sensitivity to reward. We found that the development of obesity in rats is associated with the emergence of a profound brain reward deficit, measured by elevated LH self-stimulation thresholds in rats3. In addition, obese rats demonstrate markedly reduced willingness to work for food rewards. Precisely how LH influences brain reward function and the value of food, and by extension its role in obesity, remains unclear. The habenula is a distinct set of nuclei linking forebrain and midbrain structures and is divided into two principal parts termed the medial habenula (MHb) lateral habenula (LHb). The LHb has been described as a "preference center" which exerts a negative influence over motivated behaviors through inhibition of midbrain dopamine neurons. A major input to the LHb originates in the LH, providing a potential mechanism by which the LH can influence brain reward function and the motivational value of food. Here, we tested the hypothesis that LH projections to LHb play an important role in food preference and the development of food-relevant motivational deficits in obese rats. To target the LHb-LH pathway, we delivered an AAV2/5-Cre-eYFP virus into the LHb, this travels in a retrograde fashion to express Cre recombinase in the cell bodies of LHb projecting neurons. A Cre-inducible diphtheria toxin (DTA) was then delivered to the LH, selectively ablating LH neurons that project to LHb. In a separate set of experiments we delivered Cre-inducible "excitatory" (hM3Dq) Designer Receptors Exclusively Activated by Designer Drugs (DREADD) to LH instead of Cre-inducible DTA. This allowed for stimulation of the LH-LHb circuit via administration of clozapine-N-oxide (CNO) which exclusively stimulates DREADDs. We found lesioning of the LH-LHb pathway in rats decreased the motivational value of food in a manner similar to that observed in obese rats, reflected by a decreased willingness to work for food rewards and decreased home cage chow consumption. Conversely stimulating the LH-LHb circuit increased the willingness of rats to work for food rewards and increased home-cage chow consumption. These findings identify the LH-LHb pathway as an important brain circuit involved in regulating feeding. Currently, we are seeking to identify LHb neurons that transduce food-relevant information and explore adaptive responses in this pathway that may occur during the development of obesity. 1 Finkelstein, E. A., Ruhm, C. J. & Kosa, K. M. Economic causes and consequences of obesity. Annual review of public health 26, 239-257, doi:10.1146/annurev.publhealth.26.021304.144628 (2005). 2 Olds, J. & Milner, P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. Journal of comparative and physiological psychology 47, 419-427 (1954). 3 Johnson, P. M. & Kenny, P. J. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nature neuroscience 13, 635-641, doi:10.1038/nn.2519 (2010).

The impact of neurogenesis on flexible maze training: effects on hippocampal volume and cognition. Timothy Schoenfeld1, Diane Rhee1, Heather Cameron1. 1Section on Neuroplasticity, National Institute of Mental Health. Previous research has shown that taxi cab drivers in London have larger hippocampi than non-drivers, suggesting that intense spatial training influences hippocampal growth. In addition, ablation of neurogenesis in adult rats reduces hippocampal volume, therefore we were interested in devising a rat-model of spatial-training induced hippocampal growth and exploring the effects of ablating neurogenesis on that model. To do so, we created a new maze environment, called the flex maze, a standard labyrinth with removable walls to create multiple maze environments within the same arena. We treated GFAP-TK transgenic rats and WT littermates with valganciclovir beginning at 8 weeks of age to inhibit adult neurogenesis. Rats were then trained on three different maze configurations, each with unique olfactory and visual cues, over the course of 4 weeks, were tested on an object location task, and perfused to measure hippocampal volume using a 14.1T MR scanner. Both WT and GFAP-TK rats learned various mazes at the same rate, showed spatial knowledge of the mazes in probe trials, and accurate retrieval of different mazes after all mazes had been learned. Only the maze scented with peppermint, an aversive odor for rats, showed a genotype difference, as WT rats were slower to solve this maze when switched onto it and did not retain it in subsequent retrieval trials. GFAP-TK rats had smaller hippocampi than WT controls, with significant volume decreases in the dentate gyrus and CA3. Maze-trained WT rats had larger hippocampal volumes than controls, which was fully explained by growth in ventral sections of CA1. GFAP-TK rats did not show this volume increase. In an object location task, only maze-trained WT rats showed significant object location learning, whereas all control rats and maze-trained GFAP-TK rats displayed no learning. The data suggest that both neurogenesis-intact and neurogenesis-deficient rats learn multiple spatial environments just as well, even though learning in rats without neurogenesis are not affected by aversive odors like WT controls. This spatial learning does induce growth in ventral CA1 and has positive cognitive influences in WT rats, but rats without neurogenesis do not display the volume and cognitive benefits of spatial training.

Post-weaning social isolation results in ultrasonic communication deficits, cognitive impairments and alterations in microRNA-dependent Ube3a1 function on neuronal plasticity in rodents: Implications for autism. Dominik Seffer1, Henrike Rippberger1, Jeremy Valluy2, Silvia Bicker2, Ayla Aksoy-Aksel2, Martin Lackinger2, Simon Sumer2, Roberto Fiore2, Tatjana Wüst3, Franziska Metge4, Christoph Dieterich4, Gerhard Schratt2, Rainer K. W. Schwarting1, Markus Wöhr1. 1Behavioral Neuroscience, Experimental and Physiological Psychology, Faculty of Psychology, Philipps-University of Marburg, Marburg, Germany. 2Institute of Physiological Chemistry, Biochemical-Pharmacological Center Marburg, Philipps-University of Marburg, Marburg, Germany. 3Interdisciplinary Center for Neurosciences, SFB488 Junior Group, University of Heidelberg, Heidelberg, Germany. 4Max Planck Institute for Biology of Ageing, Computational RNA Biology Lab, Cologne, Germany. Rats are highly social animals and rough-and-tumble play during adolescence has an important role for social development. Post-weaning social isolation, i.e. separation from conspecifics during this phase, is known to induce behavioral phenotypes and changes in neural development relevant to neuropsychiatric disorders like autism. Ultrasonic vocalizations (USVs) are an important component of the rat's social behavioral repertoire and serve as situation-dependent affective signals with important communicative functions. High-frequency 50-kHz USVs are produced in appetitive situations such as rough-and-tumble play and induce social approach behavior, indicating that they serve as social contact calls. Here, we tested by means of our highly standardized 50-kHz USV radial maze playback paradigm if social isolation impairs approach behavior in response to pro-social USVs. Male rats were housed in one of the following conditions: group housing, short-term isolation (24 hours), or long-term isolation (28 days). While group-housed and short-term isolated rats displayed approach behavior in response to pro-social 50-kHz USVs, post-weaning long-term isolation led to pronounced deficits, with rats rather displaying avoidance behavior. Importantly, such deficits could be reversed by one additional week of peer-rearing and were not observed after post-adolescence long-term isolation, indicating a critical period for social development during adolescence. At the neurobiological level, post-weaning isolation, also resulting in poor novel object recognition as expected, led to an increase in an alternative E3 ubiquitin ligase Ube3a transcript, Ube3a1, in the

hippocampus; a key regulator of activity-dependent synapse development and plasticity. The increase in Ube3a1 RNA expression following post-weaning isolation was paralleled by elevated levels of microRNA 134, with Ube3a1 knockdown increasing dendritic complexity in the hippocampus in wild-type controls. Ube3a1 RNA knockdown, however, failed to induce dendritic complexity when the miRNA cluster 379-410, including miR-134, was missing, demonstrating that the Ube3a1 function is microRNA-dependent. Taken together, post-weaning social isolation led to ultrasonic communication deficits, cognitive impairments and alterations in microRNA-dependent Ube3a1 function on neuronal plasticity. The finding that environmental factors affecting social behavior and cognition alter Ube3a has important implications, particularly since loss of UBE3A is the leading cause for the neurodevelopmental disorder Angelman syndrome and UBE3A duplications are among the most frequent copy number variations associated with autism.

Developmental social isolation alters expression of neural proteins in adult zebrafish. Soaleha Shams1, Diptendu Chatterjee2, Robert Gerlai1,2; 1Cell & Systems Biology Dept., Univ. of Toronto Mississauga, Mississauga, ON, Canada; 2Psychology Dept., Univ. of Toronto Mississauga, Mississauga, ON, Canada. Given the existing knowledge on its genetics and development, the zebrafish serves as an excellent translational model for studying vertebrate physiology. More recently, zebrafish has been popular in behavioral neuroscience as it is a highly social species with a wide range of quantifiable behaviors. Similar to social mammals, the early social environment of zebrafish can significantly affect their subsequent expression of behaviors and functionality of neural systems. However, the effects of social deprivation in zebrafish beyond the larval stage remain relatively unknown. To investigate this, we generated socially-deprived zebrafish and compared them to socially-reared control fish in adulthood. We exposed groups of socially-deprived and control fish to live social stimulus fish for increasing amount of time (30 min, 2hrs, 24 hrs) and recorded their behavior. The coordinates for each fish were used to calculate behavioral variables such as locomotor activity, anxiety-like behaviors, and response to social stimulus. We also compared various brain nuclei in socially deprived and control zebrafish and quantified distributions of brain proteins involved in normal brain development and activation. We measured expression of Neu-N (a neuronal marker), synaptophysin (synapse protein), N-CAM (cell-adhesion molecule), GAP-43 (axon elongation protein), BDNF (brain derived neurotrophic factor) and c-fos (neuronal activation marker) in social and isolated fish. Here we report that early social deprivation can alter anxiety-like behavior and response to social stimuli in adult zebrafish. Furthermore, compared to control fish, in socially-deprived zebrafish we observed significant changes in neural proteins involved in attention, activity, and social behavior. Our findings provide further support towards establishment of zebrafish as a suitable animal model to study the behavioral and neural consequences of developmental social deprivation. Acknowledgements: Supported by NSERC.

Dissociable roles for basolateral amygdala and orbitofrontal cortex in optimal choice behavior under conditions of reward variability. Alexandra Stolyarova1, Alicia Izquierdo1. 1 University of California, Los Angeles. All animals make choices based on expected outcome values and adjust their behavior when reward conditions change: upshifts in value facilitate, whereas downshifts suppress responding. The basolateral amygdala (BLA) and orbitofrontal cortex (OFC) both participate in outcome valuation but their specific roles in this process are frequently difficult to dissociate. In the present work we first performed computational analyses of trial-by-trial performance of OFC- and BLA-lesioned rats in pairwise discrimination reversal learning. We found a specific detrimental effect on long-term inferred outcome value resulting from OFC lesions that recapitulated the performance impairment. Conversely, BLA was uniquely responsible for setting the value update rate. This update rate was dynamically adjusted in response to experienced outcome variability in control animals, but not in BLA-lesioned rats. These results suggest that adaptive choice behavior depends on both the mean and variance of outcome distribution. To then systematically test the effect of variability on behavioral adaptations we developed a novel decision making task using touchscreen response in rats, in which outcome values were determined by normally distributed delays to reward receipt. Rats were presented with two options identical in mean (1 sugar pellet/ 10s) but different in the variance of outcome distribution (high variability, HV vs. low variability, LV). Following the establishment of stable performance, rats experienced reward

upshifts (1/ 5s with variance kept constant) and downshifts (1/ 20s) on each option independently, followed by a return to baseline conditions. Rats distributed their choices uniformly at baseline and significantly changed their preference in response to all shifts, suggesting that they were able to infer mean option values despite variability in outcomes. Critically, choice adaptations were asymmetrical: HV potentiated responses to upshifts, but dampened the effects of downshifts. To assess the OFC-BLA mechanisms of these responses, in a separate cohort of animals we evaluated reward mean- and variability-induced neuroadaptations by quantifying the region-specific expression of GluN1 and gephyrin (a reliable proxy for membrane-inserted GABAA receptors). Gephyrin was downregulated in OFC in response to experienced reward mean regardless of variability, consistent with proposed role of this brain region in inferring overall outcome values. Conversely, reward-induced GluN1 and gephyrin upregulation in BLA was variability-dependent, with the highest levels in the HV group, supporting a role for BLA in adaptations to both outcome mean and variability. Taken together, our findings demonstrate dissociable roles for OFC and BLA in dynamic outcome valuation guiding optimal choice behavior. Support: UCLA Division of Life Sciences Recruitment and Retention Fund (Izquierdo).

Aberrant Cognitive Phenotypes and Altered Hippocampal BDNF Expression Related to Epigenetic Modifications in the Shank 1 Knockout Mouse Model for Autism. A. Özge Sungur1, Magdalena C.E. Jochner1, Hani Harb2, Ayşe Kılıç2, Holger Garn2, Rainer K.W. Schwarting1, Markus Wöhr1. 1 Behavioral Neuroscience, Experimental and Physiological Psychology, Philipps-University of Marburg, 35032 Marburg, Germany. 2 Institute of Laboratory Medicine and Pathobiochemistry and Molecular Diagnostics, Philipps-University of Marburg, Marburg, Germany. Autism spectrum disorders (ASD) are a class of neurodevelopmental disorders characterized by persistent social communication deficits across multiple contexts, together with repetitive patterns of behavior. Among the most promising ASD candidate genes is the SHANK gene family, including SHANK1. To study the contribution of SHANK1 mutations to ASD symptoms throughout development, Shank1+/+, Shank1+/-, and Shank1-/- mice were compared in behavioral assays developed to detect social communication and cognitive deficits as juveniles and adults. As juveniles, social approach and recognition were evident irrespective of genotype. In contrast, object recognition was affected by Shank1 deletion, with Shank1-/- mice being severely impaired, i.e. not showing a preference for the novel object. Furthermore, a significant increase in acetylation of histone H3 at the BDNF promoter was detected in the hippocampi of Shank1-/- juveniles. These epigenetic modifications were paralleled by increased BDNF expression levels in the hippocampi of juvenile Shank1-/- mice. In adulthood, Shank1-/- males and controls displayed normal social approach, but impaired social recognition. Object recognition was additionally impaired in adult Shank1-/- males. Conversely, adult Shank1-/- females exhibited deficits in social recognition only. In summary, the present findings indicate that Shank1 deletions lead to an aberrant cognitive phenotype and an increase in BDNF expression in the hippocampus possibly due to epigenetic modifications, together with age- and sex-dependent effects on social behavior. Support: Deutsche Forschungsgemeinschaft (DFG – WO 1732/1-1).

Alcohol induced locomotor activity is mediated by dopamine D2-like receptors in zebrafish. Steven Tran1, Amanda Facciol2, Magda Nowicki2, Diptendu Chatterjee2, Robert Gerlai1, 2. 1Department of Cell & Systems Biology, and 2Psychology, University of Toronto. Alcohol addiction is a debilitating disease costing hundreds of billions of dollars annually due to lost productivity and required healthcare. Sensitivity to alcohol's stimulant effect has been identified as a risk factor for the development of alcohol addiction, yet the mechanism of this effect is poorly understood. Using zebrafish, we investigated a potential dopaminergic mechanism underlying alcohol's stimulant effect. In the current study we first demonstrate that acute exposure to 1% alcohol for 60 minutes increases locomotor activity (i.e. total distance moved) as well as whole-brain tissue levels of dopamine quantified by high precision liquid chromatography (HPLC). To investigate the mechanism of the alcohol induced increase of dopamine, we examined tyrosine hydroxylase, the rate-limiting enzyme responsible for dopamine synthesis. Enzymatic activity assays revealed that acute exposure to 1% alcohol increased the activity of tyrosine hydroxylase as measured from whole-brain tissue in vivo as well as ex vivo, in a time- and concentration-dependent manner. Western blot analysis of whole-brain tissue revealed that acute exposure to 1% alcohol also increased the expression of tyrosine hydroxylase. We further examined the

change in spatial expression of this protein in the zebrafish brain following exposure to 1% alcohol. Our preliminary analysis revealed that acute alcohol exposure increased tyrosine hydroxylase protein expression in the zebrafish brain in a region-dependent manner. To further explore the mechanistic link between alcohol induced locomotor activity and dopamine, we examined the potential role of different dopamine receptors using a psychopharmacological approach. We found that pre-treating zebrafish with haloperidol (a dopamine D2-like receptor antagonist) attenuated alcohol induced locomotor activity. To identify specific neuronal populations of dopamine D2 receptors in the zebrafish brain activated by alcohol exposure, we examined c-fos protein expression as a method of determining neuronal activation. Western blot analysis revealed that 1% alcohol induced peak c-fos expression at 90 minutes post-exposure. We are currently examining the co-localization of dopamine D2 receptors and c-fos expression in the zebrafish brain following 1% alcohol exposure. Our results identified dopamine as an important regulator of alcohol induced locomotor activity in zebrafish. In summary, our findings show that acute exposure to alcohol increases whole-brain dopamine via induction of tyrosine hydroxylase leading to activation of dopamine D2-like receptors. Funding: Research was funded by an NSERC Discovery Grant issued to Robert Gerlai, and an NSERC CGSD issued to Steven Tran.

6:00-7:00 ***Oral Session 1: Addiction.***

Readers of histone acetylation marks regulate behavioral and transcriptional responses to drugs of abuse. Gregory C. Sartor, Sam K. Powell and Claes Wahlestedt. Center for Therapeutic Innovation and Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, Florida. Alterations in epigenetic processes within reward-related brain regions is one critical factor underlying the long-lasting behavioral abnormalities that characterize addiction. Drug-induced changes in histone acetylation levels in the nucleus accumbens (NAc) is one key factor that contributes to drug-seeking behaviors. Recently, proteins involved in the readout of acetylated histones, referred to as BET bromodomain proteins (BRD2, BRD3, BRD4 and BRDT), have been shown to be important regulators of chromatin dynamics and transcriptional activity. However, their role in addiction-related phenomena remains unknown. Here, we utilized behavioral, pharmacological and molecular techniques to examine the involvement of BET bromodomains in the behavioral response to drugs of abuse. BRD4, but not BRD2 or BRD3, was significantly elevated in the NAc of mice and rats following repeated cocaine exposure and self-administration. Systemic and intra-accumbal inhibition of BRD4 with the BET inhibitor, JQ1, attenuated cocaine conditioned place preference (CPP), but did not affect conditioned place aversion, nor did JQ1 alone induce a conditioned aversion or preference. Additional behavioral tests revealed that systemic JQ1 attenuated conditioned place preference to other psychostimulants but not morphine. Investigating the underlying mechanisms, we found that repeated cocaine administration enhanced binding of BRD4, but not BRD3, to the promoter region of Bdnf in the NAc, while systemic injection of JQ1 reduced expression of Bdnf and other genes in the NAc. Together, these findings indicate that disrupting the interaction between BET proteins and their acetylated-lysine substrates may provide a new therapeutic avenue for the treatment of psychostimulant dependence.

Ventral tegmental area L-type calcium channel mechanisms mediating cue-induced cocaine-seeking. Nii A. Addy1,2,3, Eric J. Nunes1, Shannon M. Hughley1, Wojciech B. Solecki1,4, Robert J. Wickham1,3, Keri M. Small1, and Anjali M. Rajadhyaksha5,6. 1Department of Psychiatry, Yale School of Medicine, New Haven, CT 06511, 2Department of Cellular and Molecular Physiology,3Interdepartmental Neuroscience Program, Yale University, New Haven, CT 06511, 4Department of Molecular Neuropharmacology, Institute of Pharmacology PAS, Krakow 34-343, Poland. 5Department of Pediatrics, 6Feil Family Brain and Mind Research Institute, Weill Cornell Medical College of Cornell University, New York, NY. Cue-induced drug-relapse during periods of abstinence is a major barrier to the treatment of substance use disorders. We previously demonstrated that phasic dopamine (DA) activity in the ventral tegmental area (VTA) to nucleus accumbens (NAc) pathway is necessary and sufficient for cue-induced cocaine-seeking behavior. L-type calcium channels (LTCCs) in the VTA have also been shown to regulate phasic DA activity. However, it is unclear whether VTA LTCC mechanisms mediate cue-induced drug-seeking after drug self-administration and abstinence. We used behavioral pharmacology and in

vivo voltammetry in awake, behaving rats to determine whether VTA LTCC regulation of phasic DA activity mediates cue-induced cocaine-seeking. Male, Sprague-Dawley rats received 10 days of cocaine self-administration training (~0.5 mg/kg/infusion, FR1 schedule), followed by 10 days of forced abstinence. On withdrawal day 10 (WD10), intra-VTA infusion of the LTCC antagonists, nifedipine (10 □g/side) or isradipine (74 pg or 223 pg/side), significantly decreased cue-induced cocaine-seeking. In contrast, VTA infusion of nifedipine (10 □g/side) or isradipine (223 pg/side) did not alter cue-induced sucrose-seeking. In addition, VTA isradipine (223 pg/side) did not alter the maintenance of cocaine self-administration. Previous work has shown that activation of VTA acetylcholine receptors induces phasic DA activity in an LTCC-dependent manner. Similar to isradipine, we found that VTA infusion of the nicotine acetylcholine receptor (nAChR) antagonist, mecamylamine (10 □g or 30 □g/side), dose-dependently attenuated cue-induced cocaine-seeking and that co-administration of mecamylamine and isradipine decreased cocaine-seeking to the same extent as administration of either drug alone. Using in vivo voltammetry in awake, behaving rats after cocaine self-administration and abstinence, we also demonstrated that presentation of a cocaine-associated cue led to a time-locked increase in phasic DA release in the NAc core. In ongoing experiments, we are determining whether pharmacological blockade of VTA LTCCs and nAChRs alters phasic DA responses to cocaine-associated cues. Together, our data reveals that VTA LTCC blockade robustly and specifically attenuates cue-induced cocaine-seeking, and not cue-induced sucrose-seeking, and suggests that VTA LTCCs and nAChRs may mediate cue-induced cocaine-seeking through common pathway regulation of phasic DA signaling. This work was supported by National Institutes of Health (NIH) grants DA038048 (EJN, AMR and NAA), R25 GM104553 (SMH), and MH014276 (KMS).

Prenatal testosterone activity determines adult alcohol drinking and morphology in male and female mice. Sabine E. Huber, Bernd Lenz, Johannes Kornhuber, Christian P. Müller. Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany. An accepted marker for prenatal sex hormone exposure is the second-to-fourth-digit ratio (2D:4D). It was shown that the 2D:4D ratio can be altered in mice by modification of the prenatal hormonal balance. Moreover a recent study demonstrated that alcohol-dependent patients exhibited reduced 2D:4D ratio. This suggests that prenatal sex hormones might influence the development of alcohol addiction. The aim of our study was to investigate the role of prenatal dihydrotestosterone (DHT) and flutamide (an androgen receptor antagonist) administration on alcohol addiction and mouse morphology. Prenatally treated offspring of CD1 dam mice were tested in a two-bottle choice paradigm with increasing alcohol concentrations (2 – 16 vol%). Following the test for addictive behavior was a taste preference test, with either a sweet (0.5 and 5% sucrose) or a bitter (2 and 20 mg quinine) solution. The 2D:4D ratio was analyzed using GIMP software on scans of the paws and head size, body and tail length were measured. Prenatal androgen receptor inhibition by flutamide led to a decrease in alcohol consumption, preference and total fluid intake in males, as well as to a reduced alcohol preference, but increased water consumption, in females. Prenatal activation of the androgen receptor by DHT, in females, increased alcohol drinking and preference, while in males it enhanced the water and total fluid intake. In females, all receptor modification groups showed an increased total fluid intake. No differences between treatments and sex could be detected in the preference of sweet taste or avoidance of bitter taste. Androgen receptor activation led to a higher 2D:4D ratio in male hind paws (left and right paw taken together), while in females a reduced 2D:4D ratio in hind paws could be observed following prenatal receptor inhibition. Prenatal treatment with flutamide increased head size and body length in males, in females, however, it decreased tail length. Decreased body and tail length could be measured in females treated with prenatal DHT. In conclusion, we could show that prenatal androgen receptor activation is required for the full expression of adult alcohol drinking behavior in mice. Furthermore we found a double dissociation in the role of prenatal androgen receptor activity for adult alcohol vs. water drinking motivation in males and females.

Ceftriaxone and cocaine relapse: Contrasting the roles of xCT and GLT-1 upregulation. Lori A. Knackstedt1. 1 University of Florida, Gainesville, FL, USA. Ceftriaxone is a beta-lactam antibiotic which increases the expression and function of the glutamate transporter GLT-1 and of system xC- (Sxc), which

exchanges extracellular cysteine for intracellular glutamate. Basal glutamate levels in the NA (NA) are largely controlled by Sxc and a decrease in its activity is a contributing cause of the altered glutamate homeostasis observed in this brain region following cocaine self-administration in rats. The catalytic subunit of Sxc is xCT, and we have demonstrated that expression of xCT and GLT-1 is decreased in the NA core following cocaine self-administration. We have also shown that ceftriaxone attenuates cue- and cocaine-primed reinstatement while restoring levels of both xCT and GLT-1 in the NA core. At this time it is not known if alterations in both transport systems mediate the altered synaptic plasticity in the NA after cocaine self-administration. Here we used a morpholino antisense strategy to decrease the expression of xCT protein and examined basal levels of glutamate and GluA1 and GluA2 expression. We found that xCT antisense infusion into the NA core significantly decreased basal glutamate. We also found an increase in NA GluA1 expression in cocaine self-administering rats and no change in GluA2 expression. In rats that had self-administered cocaine and received intra-NAc infusion of xCT antisense, this increase in GluA1 was potentiated. In a separate group of rats, we utilized a viral vector to selectively upregulate glial GLT-1 expression in the NA core and found no impact on the reinstatement of cocaine-seeking. GLT-1 upregulation via AAV did not produce an accompanying increase in xCT expression. These data support the importance of xCT expression in maintaining basal glutamate in the nucleus accumbens and point to basal glutamate levels as a key mediator of post-synaptic AMPA receptor alterations. Furthermore, the upregulation of GLT-1 alone is not sufficient to suppress cocaine-seeking. Taken together, these results indicate that medications targeting GLT-1 upregulation alone will not be sufficient to reduce cocaine relapse.

Sex differences in the selection between psychostimulant and food reinforcement in rats. Tod E. Kippin, Jared R. Bagely, Mari D. Purpura, Philip A. Vieira. Department of Psychological and Brain Sciences, University of California, Santa Barbara. The etiology of addiction remains to be elucidated but, intriguingly, most individuals who consume drugs of abuse do not become addicted, indicating substantial individual differences in addiction vulnerability/resiliency in the human population. A cardinal characteristic of addiction is the choice to take drugs over other normally rewarding or important activities. Consistent with differential addiction vulnerability in humans, emerging studies demonstrate substantial individual variability in the propensity for animals to take or seek-out drugs. This presentation will describe recent studies from our group examining rats allowed to choose between concurrent psychostimulant (cocaine or methamphetamine) and food reinforcement. Our findings indicate that male rats exhibit a low preference for cocaine when forced to choose between it and food. Conversely, females exhibit a substantially higher selection of cocaine over food compared to males. Similarly, males exhibit low preference for methamphetamine over food reinforcement with females exhibiting a moderately higher level of preference for methamphetamine. In addition, the selection of cocaine versus food is modulated by estrogen in both females and males following gonadectomy. These studies suggest novel avenues for investigating the sex and individual differences in addiction as well as endocrine contributions to addiction-like behavior that are likely to inform the neurobiological bases of addiction vulnerability.

Tetrahydrocannabivarins – Cannabinoids with Strong Anti-Nicotine Effects in Multiple Rodent Models of Nicotine Dependence. Eliot L. Gardner1, Pretal Muldoon2, Xiao-Fei Wang3, Guo-Hua Bi1, M. Imad Damaj4, Aron H. Lichtman4, Roger G. Pertwee5, Zheng-Xiong Xi1. 1Molecular Targets and Medications Discovery Branch, Intramural Research Program, National Institute on Drug Abuse, Baltimore, MD, USA; 2Department of Anatomy and Neurobiology, Virginia Commonwealth University School of Medicine, Richmond, VA, USA; 3Beijing Institute of Pharmacology and Toxicology, Beijing, China; 4Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA, USA; 5Institute of Medical Sciences, University of Aberdeen, Aberdeen, Scotland, UK. Cannabinoid CB1 receptor antagonists have long been known to possess anti-addiction efficacy in animal models, against a broad range of addictive substances. More recently, selective CB2 receptor agonists have been shown to have similar efficacy in animal models. The tetrahydrocannabivarins are a class of cannabinoids exerting combined CB1 antagonist/CB2 agonist effects. We tested delta-8-tetrahydrocannabivarin (THCV) in multiple animal models of nicotine dependence to see if tetrahydrocannabivarins have promise as anti-nicotine pharmacotherapies. We tested THCV against intravenous nicotine self-administration

and against both cue-induced and nicotine-induced relapse to nicotine-seeking behavior in P rats. We also tested THCV against nicotine-induced conditioned place preference and against nicotine withdrawal in mice. THCV significantly attenuated intravenous nicotine self-administration and robustly inhibited cue-induced and nicotine-induced relapse to nicotine-seeking behavior. THCV also dose-dependently attenuated nicotine-induced conditioned place preference in mice, and significantly ameliorated nicotine withdrawal in mice. We conclude that tetrahydrocannabivarins may have therapeutic potential for the treatment of nicotine dependence. We also suggest that the tetrahydrocannabivarins be tested in preclinical animal models for possible putative anti-addiction efficacy against other addictive drugs.

6:00-7:00 ***Oral Session 2. Schizophrenia, other Genetic Disorders.***

Arc/Arg3.1 genetic disruption in mice causes dopamine system alterations and neurobehavioral phenotypes related to schizophrenia. Francesca Managò1, Maddalena Mereu2, Surjeet Mastwal3, Diego Scheggia1, Marco Emanuele1, Rosa Mastrogiacomo1, Konrad Talbot4, Maria A. De Luca5,6, Daniel R. Weinberger7,8, Kuan H. Wang3*, Francesco Papaleo1*. 1Department of Neuroscience and Brain Technologies, Istituto Italiano di Tecnologia, via Morego 30, 16163 Genova, Italy. 2Dipartimento di Scienze del Farmaco/IRCSS E.Medea, Universita' degli Studi di Padova, Largo Meneghetti 2, 35131 Padova, Italy. 3Unit on Neural Circuits and Adaptive Behaviors; Genes, Cognition and Psychosis Program, National Institute of Mental Health, Bethesda, MD, USA. 4Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, CA, USA. 5Department of Biomedical Sciences, Università di Cagliari, Italy. 6National Institute of Neuroscience (INN), Università di Cagliari, Italy. 7Lieber Institute for Brain Development, Johns Hopkins University Medical Campus, Baltimore, Maryland. 8Departments of Psychiatry, Neurology, Neuroscience and the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA. Recent human genetic studies highlighted the postsynaptic Activity-regulated cytoskeleton-associated protein (Arc) complex as a convergence signal for several genes implicated in schizophrenia. However, the functional significance of Arc in schizophrenia-related neurobehavioral phenotypes and brain circuits is unknown. Here we demonstrated that genetic disruption of Arc in mice produces deficits in sensorimotor gating, social, and cognitive abilities, as well as altered locomotor/amphetamine responses consistent with schizophrenia-related phenotypes. Furthermore, genetic disruption of Arc led to reduced frontal cortical and increased mesoaccumbens dopamine release with increased postsynaptic D2 expression in the striatum. These findings identify a previously unexpected role of Arc in the regulation of dopaminergic neurotransmission. Hypoactive mesocortical and upregulated mesolimbic systems recapitulated most of the feature state in the dopamine hypothesis of schizophrenia. Moreover known role of Arc in the glutamatergic system together with these results support the notion that Arc could be a point of convergence for the pathophysiology of schizophrenia.

Preventing both schizophrenia- and depression-like behavioral abnormalities in a novel neurodevelopmental model. Weiner I1,2, Wolff N1, Ardeli R1, Jacobovich E1, Doron R3. 1 School of Psychological Sciences and 2Sagol School of Neuroscience, Tel-Aviv University, Israel; 3Department of Behavioral Sciences, Academic College Tel-Aviv Jaffo, Israel. Over the past two decades, increasing efforts have focused on prospective identification of subjects at high risk for psychosis and affective disorders and attempts at early intervention. A critical assumption is that treatment at earlier (asymptomatic) stages is associated with better response and prognosis, and is trans-diagnostic. Although some success has been achieved, studies in humans face grave practical, methodological, and ethical problems. Animal models can aid considerably in demonstrating feasibility of prevention at the PoC level. This study used a novel neurodevelopmental model in which lactational exposure to the viral mimic poly-I:C leads to sex-specific schizophrenia and depression phenotypes in the offspring, to test the concept that dug treatment can be highly effective and trans-diagnostic when given at an asymptomatic stage. Results showed that adult male offspring of polyI:C-injected lactating dams exhibited cognitive perseveration as manifested in persistent latent inhibition (LI) mimicking negative/cognitive symptoms of schizophrenia, while female offspring exhibited depressive-like despair as manifested in increased immobility in the forced swim test (FST). Both behavioral abnormalities as well as accompanying brain

structural abnormalities were prevented by the atypical anti-psychotic risperidone (0.045mg/kg), the mood stabilizer lithium (25mg/kg) and a novel herbal treatment adaptogen (30mg/kg), if given during adolescence (postnatal day 34-47) but not in adulthood. These results support the concept that early intervention can be drug-nonspecific and transdiagnostic. Acknowledgments: This work was supported by the Israel Science Foundation (grant no. 467/11) to IW.

Evaluating the validity of a novel transgenic mouse model for neuregulin 1 type III for schizophrenia. Tim Karl1,2,3, Juan C Olaya1,2,4, David Lloyd1,2,4, Carrie L Heusner5, Mitsuyuki Matsumoto5 & Cynthia Shannon Weickert1,2,4. 1Neuroscience Research Australia (NeuRA), Sydney, NSW, Australia. 2School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia. 3School of Medicine, Western Sydney University, Sydney, NSW, Australia. 4School of Psychiatry, University of New South Wales, Sydney, NSW, Australia. 5Astellas Research Institute of America LLC, Skokie IL, USA. Neuregulin 1 (NRG1) is a well-characterized risk gene for schizophrenia (SZ). Elevations in NRG1 protein and transcripts have been found in SZ with a recent study showing that the transcript for the NRG1 type III isoform (NRG1-III) is overexpressed in the forebrain of SZ patients that carry a risk haplotype for NRG1. In light of this, a mouse overexpressing Nrg1-III specifically in the forebrain was created in order to assess how Nrg1-III overexpression might cause or contribute to SZ-related deficits thereby considering construct and face validity of this novel mouse model. Adult Nrg1-III transgenic and wild type-like control littermates of both sexes were characterized comprehensively for behaviours relevant to SZ including social and cognitive domains. Once behavioural testing was completed, brains were collected to analyse mRNA expression levels of Nrg1 type III as well as for three housekeeper genes in the prefrontal cortex (PFC) using qPCR. Nrg1-III transgenic mice were healthy and showed normal sensory abilities and neurological reflexes. Nrg1-III overexpression resulted in impaired learning of a fear-eliciting context and reduced social interaction times with a novel mouse. Furthermore, transgenic mice were characterised by deficient prepulse inhibition, one of the hallmarks of SZ mouse models. Importantly, these mice also displayed an increase in normalized Nrg1-III mRNA expression in the PFC. These findings confirm that the Nrg1-III transgenic mouse has a robust overexpression of Nrg1-III mRNA in forebrain (similar to that found in the disease state of a subset of SZ patients) and that this overexpression causes behavioural deficits, which are highly relevant to SZ. In conclusion, our results provide evidence that an overexpression of Nrg1-III may contribute to the symptomatology of SZ and that a newly developed mouse model for Nrg1-III overexpression possesses both face as well as construct validity for SZ research. We are currently determining cannabis-Nrg1 interactions in this model.

A precision medicine genetic marker for core cognitive deficits in schizophrenia. Diego Scheggia1, Maddalena Mereu2, Marco Armando3, Maria A. De Luca4, Genny Orso5 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. 3Department of Neuroscience, Bambino Gesù Children's Hospital, Piazza Sant'Onofrio 4, 00100 Rome, Italy. 4Department of Biomedical Sciences, Università di Cagliari, Italy. 5IRCCS E. Medea Scientific Institute, Conegliano, Italy. Antipsychotics are the first-line, chronic, most largely-used and costly medications for the management of schizophrenia. These drugs show massive individual variability and non-optimal efficacy, especially for schizophrenia-relevant cognitive deficits. Notably, there is no biological rationale that can predict a person's response to these treatments. Using combined and strictly translational studies in mice and humans, here we found that variations in the DTNBP1 gene, associated with reduced levels of dysbindin-1, confer better responses to antipsychotic treatments for schizophrenia core dysfunctions in executive control. Using multilevel ex vivo and in vivo approaches in genetically modified mice and drosophilae, we then established that the dysbindin-antipsychotics interaction resides in a unique potentiation of cortical dopamine/D2 signaling through the amelioration of astrocytic and presynaptic intracellular trafficking. These findings demonstrate a biological indicator for the implementation of personalized healthcare for cognitive disabilities in schizophrenia, pioneering the concrete use of pharmacogenetics to combat psychiatric disorders.

The role of mesopontine cholinergic neurons in prepulse inhibition of startle. Azzopardi, Erin; Louttit, Andrea; Haddad Faraj; Schmid, Susanne. Department of Anatomy and Cell Biology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada. Prepulse inhibition (PPI) is a pre-attentive process that suppresses sensory evoked motor responses in favor of an orienting response towards a sensory stimulus. It is hypothesized that the mechanism underlying PPI is cholinergic inhibition of startle neurons in the brain stem by cholinergic projections from mesopontine neurons, located in the pedunculopontine tegmental nucleus (PPT) and laterodorsal tegmentum (LDT). To test this, we injected transgenic rats (Chat-Cre) with either a DREADD, optogenetic (ChR2), or respective control virus into the PPT in order to transiently inactivate or activate these neurons and test the effect on startle/PPI. DREADD inhibition of mesopontine cholinergic neurons did not disrupt PPI at different prepulse levels or interstimulus intervals tested, but seems to slightly decrease baseline startle. DREADD induced inhibition did disrupt morphine conditioned place preference (CPP) as a positive control measure. Conversely, optogenetic stimulation of the PPT/LDT did not induce PPI, but rather facilitated startle in the ChR2 expressing rats. This facilitation was most robust at the ISI of 15 ms, and could be blocked by a nicotinic antagonist. Optogentic stimulation also caused CPP in ChR2 transfected rats, but not in control animals, as a positive control. Our results suggest that the cholinergic cells of the PPT may not be as critical for PPI, as generally assumed, but might rather increase startle responses in accordance to their assumed function in arousal.

Hypoglycemia Reduces Cognitive Performance with Changes of Cerebral Blood Flow in Subjects with Type 1 Diabetes. Gjedde, Albert1; Gejl, Michael2; Brock, Birgitte2; Møller, Arne2; Van Duinkerken, Eelco3; Haahr, Hanne4; Hansen, Charlotte4; Chu, Pei-Ling5; Stender-Petersen, Kirstine4; Rungby, Jørgen6. 1University of Copenhagen, Copenhagen, Denmark, 2Aarhus University and Aarhus University Hospital, Aarhus, Denmark, 3VU University Medical Center, Amsterdam, The Netherlands, 4Novo Nordisk A/S, Søborg, Denmark, 5Novo Nordisk Inc., Princeton, NJ, USA, 6Gentofte University Hospital, Copenhagen, Denmark. This randomized single-blinded, two-period cross-over trial investigated cognitive performance and associated regional cerebral blood flow (rCBF) during hypoglycemia. Subjects (n=26) with type 1 diabetes (T1D) underwent hypoglycemic and euglycemic clamps with target plasma glucose concentrations of 2.8±0.2 mM and 5.5±0.55 mM, respectively. Working memory was scored with a modified digit symbol substitution test (DSST), adjusted for sight and finger movements (control DSST [cDSST]) at both visits. During DSST and cDSST, rCBF was measured in 19 pre-specified brain regions with positron emission tomography of tracer water uptake. DSST scores and response times were analyzed using a linear mixed-effect model with glycemic condition and period as fixed factors and subject as random factor. All rCBF values were normalized to cerebral cortex and we compared these values by ANOVA with glycemic condition, period, and subject as fixed factors. DSST scores were significantly lower (estimated treatment difference [ETD]: –0.63, P=0.014) and the response times significantly longer (ETD: 2.86 s, P=0.0126) in hypoglycemia vs euglycemia. During DSST, rCBF was significantly lower (P<0.05) in medial temporal lobe and hippocampus, and significantly higher (P<0.05) in dorsolateral prefrontal cortex, middle and inferior frontal gyrus, superior parietal lobe and thalamus during hypoglycemia vs euglycemia. During cDSST, rCBF measures were significantly lower (P<0.05) in hippocampus, medial temporal lobe, parahippocampal gyrus and striatum, and significantly higher (P<0.05) in the regions of the frontal lobe, orbitofrontal cortex, superior frontal gyrus, ventromedial prefrontal cortex, superior parietal lobe and thalamus during hypoglycemia vs euglycemia. When the DSST was adjusted for control movement (DSST–cDSST), rCBF was elevated only in the striatum during hypoglycemia vs euglycemia. We conclude that even hypoglycemia at plasma glucose levels just below 3.1 mM reduced cognitive performance, accompanied by significant changes of rCBF, indicating raised activity in the attention network, at the expense of activity in the default mode network.

Thursday, June 9

8:00-10:00 ***Behavioral and molecular bases of drug and food addiction: Similarities and Differences.*** Chair: Jean Lud Cadet.

Compulsive palatable food eating in the presence of adverse consequences. Cadet, Jean Lud; White, Shannan; Krasnova, Irina. Molecular Neuropsychiatry Research Branch, NIDA Intramural Research Program, NIH/DHHS, Baltimore, MD. Addictions are major public health problems because of adverse medical and neurological consequences. Recent data have suggested that food and drug addiction may share some basic neurobiological substrates. These similarities include involvement of brain reward pathways and activation of similar neurotransmitter systems. However, it is also clear that the majority of patients who are addicted to food are not addicted to drugs, thus suggesting that differences in basic mechanisms might trigger different clinical manifestations and outcomes. In our laboratory, we have recently developed rat models of methamphetamine and food self-administration that we are investigating in parallel. Administration of palatable food and methamphetamine is very robust, with rats escalating their intake over the first 10 days of exposure. The use of footshocks as adverse consequences helped to segregate rats into a group of food-addicted rats that continue to press a lever for food and another group of non-addicted rats that stop their food seeking behaviors. Similarly, footshocks also helped to segregate abstinent and compulsive methamphetamine takers. Interestingly, higher levels of footshocks are required to dichotomize food rats into the two distinct phenotypes, suggesting that, in rats, palatable food may be more addictive than methamphetamine. These two models are presently being used to identify and compare the neurobiological substrates of food and methamphetamine addiction. Funding: This research was supported by the Intramural Research Program of NIDA/NIH.

Molecular mechanisms underlying methamphetamine addiction and relapse. Irina N. Krasnova, Ph.D. Molecular Neuropsychiatry Research Branch, National Institute on Drug Abuse, NIH, DHHS, Baltimore, MD, USA. One of the main problems in the treatment of methamphetamine (METH) addiction is a high rate of relapse to drug use after abstinence. Evidence has accumulated to show that neuroplastic changes in the striatum and hippocampus may play critical roles in drug-taking behavior and relapse to drug use. Recently, we developed a model of METH self-administration with electric foot shock in rats that resembles clinical situation in humans. This model allows to differentiate animals that stop self-administration of the drug facing negative consequences (shock-sensitive rats), from those that continue to self-administer METH and develop addiction (shock-resistant rats). Here, we studied whether shock-sensitive and shock-resistant rats show differences in relapse to METH seeking after abstinence and neuroplastic changes associated with increased vulnerability to drug relapse. We trained rats to self-administer METH (0.1 mg/kg/ infusion) for 9 h/day for 20 days. Subsequently, 50% of METH infusions were accompanied by mild foot-shock (0.18 ->0.36 mA, 0.5 sec) for 10 days. A control group of rats self-administered saline. We found that 55% of shocked animals reduced METH self-administration to about 20% of pre-shock level, whereas the remaining animals continued to self-administer the drug (>50% of pre-shock level) in spite of electric foot-shocks. We accessed cue-induced METH seeking in 1-h relapse tests on withdrawal days 2 and 21. We found higher cue-induced METH seeking on withdrawal day 21 than on withdrawal day 2 in all drug self-administration groups. However, shock-resistant rats showed 4-times higher METH seeking on withdrawal day 21 than shock-sensitive animals. Next, we studied transcriptional and neuroplastic changes in the hippocampi and striata of shock-resistant and shock-sensitive rats using RNA sequencing, RT-PCR and Western blot. We found increases in CREB binding protein and histone acetyltransferase 1 mRNA levels in the striatum of shock-resistant animals in comparison to shock-sensitive and control rats. In addition, we observed decreases in FosB and HDAC5 mRNA levels in the striatum of shock-sensitive animals. We also found decreases in dopamine D1 receptor, HDAC9 and HDAC10 mRNA and protein levels in the hippocampus of shock-sensitive animals in comparison to control and shock-resistant rats. Our findings suggest that these transcription factors

and epigenetic enzymes may be important substrates for the relapse to METH self-administration. This research was supported by NIDA-IRP.

Sign-tracking; A failure in flexibility. Helen M. Nasser1,2, Yu-Wei Chen1, Kimberly Fiscella1, Donna J. Calu1,2. 1Behavioral Neuroscience Research Branch, Intramural Research Program, NIDA, NIH, DHHS, Baltimore, MD, USA. 2Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, MD, USA. The behavior of addicted individuals is characterized by a heightened motivation for drugs and an inflexibility characterized by a persistence to seek and take drugs despite negative consequences. Sign-tracking rats that approach and engage a food-associated lever cue subsequently display heightened motivation for drug-associated cues. Sign-tracking rats also inflexibly respond to drug-cues despite punishment. We explored the possibility that the heightened motivation and inflexibility of sign-trackers is rooted in individual differences in Pavlovian incentive learning prior to drug-exposure. We found that sign- and non-sign-trackers were similarly able to acquire and use the incentive value of a first order cue to support higher-order conditioning. We found that sign-trackers failed to flexibly reduce responding to a cue associated with a devalued outcome. While both tracking groups similarly attribute appetitive incentive value to Pavlovian cues, sign-trackers are unable modify behavior when the outcome values change. We investigate brain circuits mediating tracking related-individual differences in behavioral flexibility and discuss behavioral insights with relevance to addiction and cognitive strategy. NIDA-IRP support and departmental support of Anatomy and Neurobiology, University of Maryland, School of Medicine.

Environmental enrichment and addiction. Marcello Solinas 1,2. 1 INSERM, U1084, F-86022 Poitiers, France. 2 Université de Poitiers, U1084, F-86022 Poitiers, France. Accumulating evidence indicates that environmental enrichment (EE) has powerful beneficial effects on drug addiction. In fact, exposing animals to EE during adolescence decreases the rewarding effects of drugs in conditioned place preference procedures and reduces cocaine self-administration at adulthood. In addition, exposure to EE during periods of abstinence from drugs eliminates already developed addiction-like behaviors and to reduce the risks of relapse. Importantly, the effects of EE appear to generalize to food seeking under similar experimental conditions. These preventive and curative effects of EE are associated with neuroadaptations such as alteration of neurotransmitter levels, changes in gene expression and transcription factors, chromatin rearrangement, and stimulation hippocampal neurogenesis in several brain areas. These effects could be a result of a stress-inoculation mechanism in which repeated EE-induced arousal would results in more efficient ability to deal with subsequent stressful life events. In turn, this would allow individuals to better control their impulses and resist craving for drugs.

8:00-10:00 ***Diet impact on brain plasticity and cognition.*** Chair: Guillaume Ferreira; Co-Chair: Patrizia Campolongo.

Juvenile obesity bidirectionally modulates amygdala and hippocampal memory systems. Guillaume Ferreira 1,2. 1 Nutrition and Integrative Neurobiology lab, INRA, France; 2 Bordeaux University, France. The obesity pandemic is linked to cognitive disorders in humans. Growing prevalence of obesity during adolescence is particularly alarming since it is a decisive period for maturation of the hippocampus and the amygdala, both required for neurocognitive shaping required for the whole life duration. Here, we evaluate 1) the potential higher vulnerability of adolescence to the effects of obesity on hippocampal and amygdala-dependent memory systems and 2) the mechanisms involved. Using behavioral, cellular imaging and electrophysiological approaches, we were able to demonstrate that high-fat diet (HFD)-induced obesity during adolescence (i.e. exposure from weaning to adulthood) has more impact on memory and plasticity than HFD at adulthood. Surprisingly, adolescent obesity affects both memory and plasticity in a bidirectional way, impairing hippocampal function (Boitard et al., Hippocampus 2012, BBI 2014) but enhancing amygdala function (Boitard et al., JN 2015). As potential mechanisms, we found a potentiated inflammatory response specifically in the hippocampus that could explain decreased hippocampal function (Boitard et al., BBI 2014). We also demonstrated that deregulation of hypothalamo-pituitary-adrenal (HPA) axis induced protracted release of glucocorticoids that is responsible for increased

amygdala plasticity and memory (Boitard et al., JN 2015). More recently we found that hippocampal endocannabinoids, presumably through glucocorticoids interaction, mediate HFD-induced memory alterations. Altogether these results suggest that adolescence represents a period of increased susceptibility to the effects of diet-induced obesity that may promote maladaptive cognitive processing later in life.

Effect of stress and high-fat diet on extinction memory and prefrontal plasticity in postweaning and adult animals. Mouna Maroun1, Guillaume Ferreira2, Rachel Schayek1, Tala Khazen1, Idit Mor1, Sophie Trabish1, Walaa Awad1, Milly Kritman1. 1 Sagol Department of Neurobiology, University of Haifa, Haifa, Israel. 2 UMR1286 INRA, Université Bordeaux2; Bordeaux, France. Juvenility is a critical developmental stage during which the medial prefrontal cortex (mPFC) undergoes major changes and the brain is vulnerable to the effects of stress. Surprisingly, the engagement of the mPFC in extinction of fear was reported to be identical in juvenile and adult animals. We recently showed that at least, stress differentially modulates extinction and plasticity in the mPFC in juvenile and adult animals (Schayek and Maroun, 2015). Specifically we showed that exposure to stress is associated with enhanced extinction and enhanced LTP in juveniles, in contrast to its effects in adult animals that our group and others have previously reported (e.g.Izquiredo et al., 2006; Akirav et al., 2009; Maroun et al., 2013). These results point to significant differences between young and adult brains, and suggest that juvenile's brain is more protected than the adult's brain under moderate levels of stress. Juvenility represents a period of increased susceptibility to effects not only to stress but also to metabolic changes. For example, diet-induced obesity during juvenility can result in maladaptive emotional processing later in life. In a recent work (Boitard et al., 2015) the effects of exposure to high fat diet (HFD) at juvenility was compared to exposure at adulthood on amygdala-dependent emotional memory and plasticity. We found that, juvenile exposure to high-fat diet (jHFD), from weaning to adulthood, enhanced long-term emotional memories and BLA plasticity through the activation of the HPA axis. These effects were not observed when adult animals were fed on similar diet. In my talk, I will present recent evidence that shows the consequences of very brief and acute exposure to HFD at weaning on extinction of fear and plasticity in the hippocampus and the BLA-mPFC pathway. Overall, our results show that short exposure to HFD mimics the effect of stress in juvenility and leads to similar effects as those observed following stress. Together, our results suggest that the juvenile’s brain is differently rewired than the adult’s brain following environmental and metabolic challenges.

Perinatal exposure to omega-3 fatty acid imbalance leads to enduring memory alterations in rats. Colucci Paola1; De Castro Valentina1; Peloso Andrea1; Campolongo Patrizia1. 1Department of Physiology and Pharmacology. Sapienza University of Rome. Rome. Italy. Growing evidence shows that long-chain omega-3 fatty acids are crucially involved in brain development and function. Omega-3 fatty acids are extensively added in large amount to several food products and particularly in newborn and infant aliments. Preclinical data show that chronic dietary omega-3 fatty acid deficiency induces behavioral alterations in rodents. Only few studies, instead, have examined the effects of omega-3 fatty acids supplementation on cognitive performances. Therefore, the aim of the present study was to investigate whether chronic dietary omega-3 deprivation or supplementation, during perinatal period, adolescence and adulthood, could affect brain development and function with emphasis on cognitive and emotional processes. The offspring of Sprague Dawley rats, fed with a omega-3 enriched or omega-3 deficient diet throughout mating, pregnancy and lactation, were subjected to a isolation-induced ultrasonic vocalization (USV) emission test and their emissions were compared with calls emitted by normal-nourished pups (control group fed with a diet with balanced omega-3 omega-6 ratio). At PND13, pups from the three exposure groups were tested in the homing test. Adolescent and adult offspring were subjected to the open-field test, elevated plus maze, inhibitory avoidance, and object recognition tests. Significant differences between rats fed with omega-3 enriched or omega-3 deficient diet and the control group were found in USV emission, elevated plus maze and object recognition tests. The present findings suggest that not only a deficiency but also a supplementation of omega-3 fatty acids could induce detrimental effects on brain development leading to enduring behavioral alterations.

The influence of diet and learning on the internal versus external controls of intake. Terry L. Davidson, American University, Washington DC. Obesity is often considered to result when food-related cues in the environment gain the capacity to overwhelm internal cues that normally regulate food intake. How this shift from external relative to internal control occurs remains to be specified. This talk will describe how the "western-diet" can alter the physiological and associative mechanisms that maintain a balance between the environmental events that excite eating and appetitive behavior and interoceptive signals that normally inhibit those responses. Specifically, evidence will be presented that links the inhibitory control of food intake and behavior instrumental to obtaining food to the hippocampal-dependent utilization of information provided by satiety signals. In contrast, the hippocampus is not involved with the ability of environmental food-related cues to evoke those eating or appetitive behavior. Data will also be presented which shows that a diet high in saturated fat and sugar (a.k.a., the Western diet) can induce pathological changes that impair hippocampal functioning. Additional findings will show that this impairment can reduce behavioral control of appetitive behavior by interoceptive satiety cues relative to that exerted by environmental stimuli. Considered together, this research outlines a potential mechanism to explain how the salience of internal satiety signals is reduced relative to food-related external cues in the control of appetitive and eating behavior. This research was supported by NIH grant R01HD028792 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development.

10:30 **Keynote: K.P. Lesch, MD, PhD;** Clinical Research Unit on Disorders of Neurodevelopment and Cognition, Division of Molecular Psychiatry, Center of Mental Health, University of Wuerzburg, Wuerzburg, Germany and Dept. of Translational Neuroscience, School for Mental Health and Neuroscience (MHeNS), Maastricht University.

Translating genetics findings into biological mechanisms for ADHD through animal models. The substantial heritability of ADHD is well documented and recent genome-wide risk gene analyses revealed synaptic cell adhesion molecules (e.g. cadherin-13, CDH13; atrophilin-3, LPHN3), glutamate receptors (e.g. metabotropic glutamate receptor-5, GRM5) and mediators of intracellular signalling pathways (e.g. nitric oxide synthase-1, NOS1). These genes encode principal components of the molecular machinery that connects pre- and postsynaptic neurons, facilitates glutamatergic transmission, modulates GABA-glutamate-dopamine system crosstalk, controls synaptic plasticity and empowers intersecting neural circuits to process and refine information. Given the currently high rate of gene discovery it is a desiderate to develop animal models of ADHD in order to better understand its aetiology and improve the treatment options that are available. Here, I will first highlight a mouse model of Cdh13 deficiency. CDH13, a unique GPI-anchored member of the cadherin family of cell adhesion molecules, has consistently been identified as a risk gene for ADHD and various comorbid neurodevelopmental and psychiatric conditions, including depression, substance abuse, autism spectrum disorder and violent behavior, while the mechanism whereby CDH13 dysfunction contributes to pathogenesis remains poorly understood. We explored CDH13's potential role in the inhibitory modulation of brain activity by investigating synaptic function of GABAergic interneurons. Cellular and subcellular distribution of CDH13 was analyzed in the murine hippocampus and a mouse model with a targeted inactivation of Cdh13 was generated to evaluate how CDH13 modulates synaptic activity of hippocampal interneurons and behavioral domains related to ADHD-like phenotypes. We found that CDH13 expression in hippocampus is confined to distinct classes of interneurons. In particular, CDH13 is expressed by many parvalbumin and somatostatin-expressing interneurons located in the stratum oriens, where it localizes to both the soma and the presynaptic compartment. Findings in Cdh13-/- mice show an increase in basal inhibitory, but not excitatory, synaptic transmission on cornu ammonis field 1 (CA1) neurons. Associated with these alterations in hippocampal function, Cdh13-/- mice display deficits in learning and memory. In addition, I will explore how we can develop zebrafish as a translational model for ADHD. In order to validate the link between the adhesion-G protein-coupled receptor LPHN3 and ADHD, and to understand the function of LPHN3 in the etiology of

the disease, we examined its ortholog lphn3.1 during zebrafish development. Loss of lphn3.1 function causes a reduction and misplacement of dopamine-positive neurons in the ventral diencephalon and a hyperactive/impulsive motor phenotype. The behavioral phenotype can be rescued by the ADHD treatment drugs methylphenidate and atomoxetine. Taken together, our results indicate that CDH13 is a negative regulator of inhibitory synapses in the hippocampus and that LPHN3 contributes to the development of the brain dopaminergic circuitry, thus providing new insights into how alterations in CDH13 and LPHN3 function may contribute to the dopamine system-moderated excitatory/inhibitory imbalance observed in ADHD.

1:30-3:30 ***Reslilience Redux: Better living through neurobiological research.*** Chair: Kelly Lambert.

Does BDNF promote or prevent behavioral responses to social stress? Kim L. Huhman, Ph.D. Neuroscience Institute, Georgia State University. Social stress is prevalent in today's society, and exposure to this stress can cause or exacerbate neuropsychiatric diseases such as posttraumatic stress disorder, depression, and social anxiety disorder. Existing treatment options are too often not effective in providing relief for these disorders. Our laboratory studies a behavioral response to social stress in Syrian hamsters, which we have termed conditioned defeat. In this model, hamsters are exposed to a brief social defeat stressor. This exposure dramatically changes ongoing social behavior such that a defeated hamster no longer displays species-typical territorial aggression but instead produces only submissive and defensive behaviors, even toward a non-threatening conspecific. Defeated animals also display numerous behavioral changes that closely resemble signs and symptoms of depression or anxiety in humans (e.g., enhanced startle, changes in ingestive behavior, marked social avoidance). The goal of our research is to characterize the neural circuit that mediates conditioned defeat and to identify the neurochemical and molecular changes that mediate this behavioral "switch" from aggression to submission. Brain-derived neurotrophic factor (BDNF) is necessary for fear learning, suggesting that BDNF promotes stress-related responding. On the contrary, BDNF increases following administration of antidepressant drugs, and this increase is necessary for the antidepressant action of these treatments. Thus, there are data that support both a "pro-stress" (i.e., susceptible) and an "anti-stress" (i.e., resilient) action of BDNF. We have demonstrated that peripherally administered BDNF TrkB receptor agonists reduce conditioned defeat, while TrkB receptor antagonists enhance conditioned defeat. These effects appear to be mediated, at least in part, in the basolateral amygdala and medial prefrontal cortex. In addition, social experience may impact BDNF systems via epigenetic regulation of BDNF gene expression. We are currently testing the hypothesis that BDNF can have both resilience-promoting and resilience-preventing actions depending on where in the brain it acts. Supported by NIMH award R01MH062044. The content is solely the responsibility of the author and does not necessarily represent the official view of the NIH.

Stimulation of Entorhinal Cortex-Dentate Gyrus Circuitry is Antidepressive. Amelia J. Eisch1, Sanghee Yun1, Ryan P. Reynolds1, Phillip D. Rivera1, Amir Segev1, Naoki Ito1, Shibani Mukherjee1, Devon R. Richardson1, Catherine E. Kang2, Dane M. Chetkovich2, Said Kourrich1.1Psychiatry Dept, UT Southwestern Medical Center, Dallas, TX 75390, USA.2Neurology and Clinical Neurosciences Dept, Northwestern University, Chicago, IL 60611, USA. Major Depressive Disorder (MDD) is considered a "circuitopathy", and brain stimulation therapies hold promise for ameliorating MDD symptoms, including hippocampal dysfunction. It is unknown if stimulation of upstream hippocampal circuitry, such as the Entorhinal Cortex (Ent), is antidepressive, although Ent stimulation improves learning and memory in lab animals and humans. Here we show molecular targeting (Ent-specific knockdown of a psychosocial stress-induced protein) and chemogenetic stimulation of Ent neurons are antidepressive. Mechanistically, we also show Ent stimulation-induced antidepressive-like behavior relies on the generation of new hippocampal neurons. Thus, controlled stimulation of Ent hippocampal afferents is antidepressive via increased adult hippocampal neurogenesis. These findings emphasize the power and potential of Ent glutamatergic afferent stimulation - previously well known for the ability to influence learning and memory - for MDD treatment. Funding: NIH, NASA.

Role of inflammatory factors and microRNAs in resilience to stress. Seema Bhatnagar, Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine. Stress induces vulnerability to psychiatric disorders only in a sub-population of individuals as others remain resilient to the effects of stress. We are interested in identifying the neural substrates through which vulnerability or resilience to stress are mediated is critical for the development of prophylactic and treatment strategies for stress-related psychiatric disorders. In addition, we are interested in identifying non-invasive biomarkers that predict vulnerability or resilience to future stress or reflect ongoing vulnerability our resilience. We have determined that vulnerability in a rat model of chronic social defeat is associated with pro-inflammatory processes in the ventral hippocampus. Vulnerability can be mimicked by pro-inflammatory cytokines and reversed if pro-inflammatory cytokines are blocked. Furthermore, panels of microRNAs in blood can predict future vulnerability or reflect ongoing resilience to social defeat and to sleep deprivation. These results suggest that microRNAs are useful biomarkers for identifying individuals that may be vulnerable to subsequent stress.

Who Moved My Cheese? Mapping resilient neurobiological response profiles to cognitive uncertainty and environmental threats. Kelly G. Lambert, Department of Psychology and Behavioral Neuroscience, Randolph-Macon College, Ashland VA USA. With depression currently considered one of the most prevalent disorders in the world, identification of approaches that build resilience against the emergence and maintenance of depressogenic symptoms is critical (Ledford, 2014). Compared to the 22-40% treatment effectiveness rates for pharmacological approaches, cognitive-behavioral therapy outcome effectiveness scores range from 42-66% (Anthes, 2014). Accordingly, several cognitive approaches such as cognitive reappraisal and cognitive flexibility have been associated with the maintenance of emotional resilience and avoidance of emotional dysregulation (Gotlib & Joormann, 2010). In an attempt to systematically investigate the influence of specific cognitive strategies on responses associated with emotional resilience, we have developed a rat model focusing on contingency-training. Although most of our research has focused on males, ongoing investigations include females and will be addressed where appropriate. In this effort-based reward (EBR) model, following 6 weeks of training during which physical effort (digging) is associated with desired outcomes (pieces of sweet cereal), animals are assessed for evidence of emotional, behavioral and neurobiological resilience (Lambert, 2006). Contingency-trained rats appear to be less vulnerable to emotional dysregulation by exhibiting higher DHEA/CORT ratios than non-contingent rats. Further, in a cognitive task assessing responses to uncertainty, or prediction errors, contingent-trained rats exhibit enhanced memory, fewer interrupted responses and increased rates of rearing (associated with information gathering) than non-contingent trained animals (Lambert et al., 2014). Diminished fos-immunoreactivity (ir) in the habenula and insular cortex have also been associated with resilience factors in the contingency-trained animals (Bardi et al., 2012). In a novel problem solving task, contingent-trained animals direct more attention to the task than non-contingent animals. Focusing on predisposed coping strategies, flexible coping rats respond to prediction errors with less fos-ir in the basolateral amygdala and insular cortex than passive and active copers. Further, flexible copers exhibit higher DHEA/CORT ratios and enhanced behavioral modifications following exposure to repeated swim stress, responses that may be associated with enhanced dentate gyrus doublecortin- and amygdala NPY-ir in flexible copers (Kent et al., 2015; Lambert, 2014). Interestingly, exposing the more resilient flexible copers to non-contingent training diminished evidence of resilience observed in the contingent-trained flexible coping animals. Thus, the ability to recalibrate and respond in an adaptive manner during uncertain situations may lead to less emotional dysregulation when exposed to more certain threats and, accordingly, less susceptibility for markers of psychiatric illness. Supported by NIMH award 1 R15 MH101698-01A1 to KGL.

1:30-3:30 ***Neuroendocrine Regulation of Animal Vocalization.*** Chair: Cheryl Rosenfeld; Co-Chair: Frauke Hoffmann.

Heeding the Hormonal Call: Turning on and Tuning in to Acoustic Signals. Andrew H. Bass. Cornell University. Reproductive imperatives rely on mechanisms enabling the successful performance of mating and related behaviors, including those dependent on acoustic communication. Acoustic communication

relies on a the ability of a sender to generate a meaningful signal and a receiver's ability to detect, interpret and respond appropriately to that signal. Enhanced coupling between the physical properties of a signal, in this case vocal, and the sensory detection, in this case auditory, of those properties are part of the reproductive strategy of many vertebrate lineages. While seasonal changes in sound production and hearing are well known especially among non-mammals, the hormonal, neurophysiological and molecular mechanisms determining this form of neurobehavioral plasticity remain largely unexplored. Vocalizing teleost fish offer highly tractable model systems for addressing these mechanisms. In particular, the plainfin midshipman (Porichthys notatus) has provided a well-established neuroethological model to identify neural mechanisms of hormone and reproductive dependent vocal and auditory plasticity. Midshipman produce pulsatile calls during social interactions that are under the control of a descending vocal network comparable in organization to networks in birds and mammals. Neuroanatomical and neurophysiological analyses indicate that several nodes in the vocal network are the targets of both steroid and neuropeptide hormone actions that lead to the production of distinct acoustic signals during the breeding season, including advertisement calls. Neurophysiology shows that seasonal, reproductive-related changes in the spectral content of advertisement calls are matched to increases in the frequency sensitivity of the saccule, the auditory division of the inner ear. Treatments of non-reproductive individuals with either estrogen or testosterone can induce a reproductive auditory phenotype. Recently, transcriptome sequencing of the vocal motor nucleus that drives sonic muscles and of the auditory hair cell epithelium has identified candidate genes underlying physiological, anatomical and molecular mechanisms driving seasonal, reproductive-related plasticity in vocal motor and auditory mechanisms. Research support from NSF IOS-1457108.

Nonclassical actions of steroids in the modulation of vocal and auditory circuits in songbirds. Luke Remage-Healey1. 1Neuroscience and Behavior Program, Center for Neuroendocrine Studies, Department of Psychological and Brain Sciences, University of Massachusetts Amherst, Amherst, MA, USA. This talk will focus on the unconventional role of steroids as neuromodulators. Traditionally, steroids are viewed as hormones secreted by peripheral glands to impact brain function and behavior over long-term timescales (days-weeks). We now understand that steroids can be synthesized by neurons at synaptic junctions, and that they can have acute (secs-mins) actions on neural circuit function and behavior. Our work in this domain focuses on auditory processing circuits in the forebrain of songbirds. We have developed evidence that brain-derived steroids can fluctuate dynamically in auditory forebrain circuits, and that steroids can have minute-by-minute actions on auditory coding and communication behaviors. Evidence from in vivo electrophysiology, patch clamp electrophysiology, in vivo microdialysis, and behavioral experiments will be discussed. Together, the evidence shows that brain-derived steroids can influence neural circuit function and sensorimotor-dependent behaviors acutely, similar to traditional neuromodulators like serotonin and dopamine.

Males mate call, females don't? – Anuran vocal communication and its hormonal control. Frauke Hoffmann1. 1Leibniz-Institute of Freshwater Ecology and Inland Fisheries, Berlin, Germany. In most anuran amphibians, both males and females vocalize. However, female vocalizations usually include release calls but no mating calls. More recently, studies investigating female anuran vocalizations demonstrated that – in some species – females are also able to utter vocalizations during mating, which are associated with coordination of courtship and amplexus. Furthermore, female frogs only initiate calling when they are close to or during oviposition, when their androgen levels are highest. Hence, it was suggested that female mating calls may have evolved by co-opting the preexisting advertisement calling pathway which appears to be common to both sexes. In males, gonadal steroids are clearly required for the display of advertisement calling and might influence calling directly by acting on vocal pathway neurons and laryngeal muscle fibers. But in addition to sexual steroids, advertisement vocalizations of male frogs can also be modulated by neuropeptides, such as arginine vasotocin (AVT), whose receptors can be found in every brain area involved in the control of frog vocalizations. More recent data further suggests that AVT can also facilitate female mate calling behavior. In this talk the vocal mating behavior of female and male anurans as well as its neuroendocrine control will be discussed.

Effects of bisphenol-A (BPA) on F2 Peromyscus californicus pup vocalizations. Johnson Sarah A.1, Javurek Angela B.1, Murphy Claire R.1, Khan Zoya Z.1, Conard Caroline M.1, Ellersieck Mark R.1, Hoffmann Frauke 2, Schenk A. Katrin 3,, and Rosenfeld Cheryl S.1. 1 University of Missouri, 2 Leibniz-Institute of Freshwater Ecology and Inland Fisheries, 3 Randolph College. Diverse rodent species elicit audible and ultrasonic vocalizations (USVs) (sounds below and above 20 kHz) as a means of communication or to initiate parental care. This may be the case in species who cannot regulate their own body temperature, such as California mice (Peromyscus californicus) which are monogamous and biparental. Prior findings suggest that as California mice pups mature and approach weaning they vocalize less and parental care decreases. We have also observed decreased parental care in F1 male and female California mice that were developmentally exposed to the endocrine disrupting chemicals, bisphenol A (BPA) or ethinyl estradiol (EE). It is not clear if the reduced parental responses are due to direct effects of these chemicals or decreased pup vocalizations by their F2 offspring. In the current study, audible vocalizations and USVs in F2 pups from F1 BPA-exposed (3 litters, 4 pups) and control parents (5 litters, 6 pups) were examined. Pups were recorded for 3 min in a sound-proof box with a high-frequency microphone. Once the recording finished, pups were placed back in the home cage with the parents and video recorded for 5 min before being placed back into the recording box where they were recorded for an additional 3 min. These recordings were performed twice per day (10.00 and 14.00 hrs) on post-natal days (PND) 2, 3, and 4 (early), 7 and 14 (mid), and 21 and 28 (late). Video recordings were analyzed to determine F1 parental responses. Preliminary results show reduced call duration in pups whose mothers were exposed to BPA (p=0.05). The average call power above 20kHz was also affected in F2 BPA-exposed pups with exposed pups showing greater call power than controls (p=0.05). Older (PND 21 and 28) BPA-exposed pups took less time to make their first call than control pups (p=0.007). At the early and mid trial periods, BPA-exposed pups also called more frequently than control counterparts (p=0.04-0.06, respectively). Initial results suggest that intergenerational exposure to BPA can disrupt aspects of pup communication.

4:00-5:00 ***Dopamine sensitization: A burden for treatments in schizophrenia?*** Chair: Davide Amato; Co-Chair: Anthony Vernon.

The acute and chronic effects of antipsychotic treatment on synaptic dopamine levels: preliminary results from a meta-analysis of microdialysis studies. Authors: Joseph Kambeitz & Davide Amato. Evidence from multiple lines of research point to a central role of alterations in dopaminergic neurotransmission in patients with schizophrenia. Consequently it is hypothesized that the clinical efficacy of antipsychotic substances results from a blockage of postsynaptic dopamine receptors. However a substantial amount of patients do not respond sufficiently to the treatment with antipsychotic medication. It has been suggested that blockage of dopamine receptors might induce adaptive processes ultimately leading to dopaminergic hypersensitivity and treatment failure of antipsychotics. Multiple previous studies have investigated changes in dopaminergic neurotransmission following antipsychotic medication in rodents using microdialysis. However there is substantial heterogeneity in the methodological characteristics of the studies that render it difficult to derive conclusions. Thus in the present work, we have conducted a quantitative review of all available microdialysis studies. We conducted a comprehensive literature research to identify all studies that applied microdialysis in rodents to measure the acute and chronic effects of antipsychotic medication on the synaptic levels of dopamine in three regions (nucleus accumbens, striatum, prefrontal cortex). Temporal trajectories of effect size measures from all studies were derived from each study and entered in a random-effects meta-analytical model. The effect of moderating variables (e.g. typical antipsychotic haloperidol vs. atypical antipsychotic clozapine, antipsychotic dosage) was investigated using meta-regression. For the analysis of the studies investigating acute haloperidol administration we identified n=15 investigating changes in the Nucleus Accumbens and n=24 studies in the Striatum. In the analysis of chronic antipsychotic administration we identified n=7 studies in the Nucleus Accumbens and n=15 studies in the Striatum. For the Nucleus

Accumbens there was a significant decrease in dopamine levels in the chronic compared to the acute condition in the time periods 0-60 ms, 61-120 ms, 121-180 ms, 181-240 ms, 240-280 ms. Similarly for the Striatum there was a significant decrease in dopamine levels in the chronic compared to the acute condition in the time periods 0-60 ms, 61-120 ms, 121-180 ms, 181-240 ms, 240-280 ms. We present preliminary results of a meta-analysis of microdialysis studies in rodents of changes in dopamine levels following acute dopamine administration. Our results demonstrate a strong decrease of changes of dopamine levels following acute administration of rodents that have undergone chronic administration of antipsychotics. Future analysis will investigate the moderating factors of different antipsychotic substances, the dosage of administered drugs and the effect of chronic administration on dopamine metabolites.

Mechansims of antipsychotic treatment failure and psychosis. Davide Amato1, Fabio Canneva2, Johannes Kornhuber1, Stephan von Hörsten2; Christian P. Müller1. 1Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany, 2Department of Experimental Therapy, Preclinical Experimental Center, Friedrich- Alexander-University Erlangen-Nurenberg, Erlangen, Germany. Hyperactive dopaminergic neurotransmission is widely seen as a mechanism of psychosis in schizophrenia. Antipsychotics are the mainstay of treatment for psychosis. However, antipsychotic treatment exhibits a poor long-term efficacy. Clinical trials have shown that the majority of treatment-responder patients will experience antipsychotic failure overtime despite receiving regular treatments. Antipsychotics-driven dopamine supersensitivity is thought to trigger a hyperactive dopamine neurotransmission, thus leading to antipsychotic treatment failure and to predispose patients to psychosis. A recognized neurobiological mechanism leading to dopamine supersensitivity is related to neuroplasticity processes disrupting dopamine D2 receptors functions. However, evidences in support of this link have not been always supported. Here, a preliminary key mechanism of dopamine supersensitivity-beyond receptor driven by antipsychotic treatment is reported. This work was supported by German ELAN grants.

Chronic antipsychotic treatment and grey matter volume loss: epiphenomenon or cause for concern? Dr. Anthony Vernon1. 1King's College London, Institute of Psychiatry, Psychology and Neuroscience, Department of Basic and Clinical Neuroscience, Psychosis Clinical Academic Group, London, UK (anthony.vernon@kcl.ac.uk). Clinical magnetic resonance imaging (MRI) studies suggest, that chronic antipsychotic drug treatment is linked to grey matter volume loss in schizophrenia patients. Studies in rodent models combining clinically comparable dosing and small animal MRI (clinically comparable technology) have provided evidence to confirm this1. However, these studies have been done in normal rats, which do not capture the innate pathology of schizophrenia, limiting the potential interpretation of these antipsychotic-induced brain volume changes. Specifically, it is unclear if these changes are related to the therapeutic efficacy of these drugs or an adverse side effect. To begin to address this question, my laboratory has begun modelling chronic antipsychotic treatment in a neurodevelopmental model relevant to schizophrenia (maternal immune activation; MIA) combined with MRI. In rats, prenatal exposure to the viral mimic poly(I:C) on gestational day 15 (GD15) leads to schizophrenia-like behavioural and MR imaging changes in the offspring2. To investigate the impact of adult antipsychotic drug treatment on brain morphometry in this model, adult poly(I:C) exposed offspring were treated with either vehicle or haloperidol (0.5 mg/kg s.c) for 4 weeks. Fixed brains from these animals were then imaged ex vivo and group-level differences in brain volume were assessed using unbiased tensor based morphometry analysis1. Relative to saline controls, poly(I:C) exposed offspring have increased volume of the frontal, sensory and parietal cortices, decreased volume of the thalamus, white matter and ventral midbrain and brainstem nuclei (q=0.05 FDR-corrected). Strikingly, adult haloperidol treatment in poly(I:C) exposed offspring normalised both thalamic and white matter volume

changes, but led to distinct volume decreases in the frontal, sensory and parietal cortices, brain stem and cerebellum, although these changes were only present at trend-level ($p<0.01$ uncorrected). These data provide preliminary evidence that antipsychotics have distinct effects on grey and white matter volume in rats pre-exposed to an immune stimulus in utero. These studies provide a mechanistic approach to begin to link brain imaging findings to neuropathology and how this might relate to adverse side effects of antipsychotics or indeed, their clinical efficacy. 1Vernon et al., Biol Psychiatry. 2014;75(12):982-90. 2Vernon et al., Eur Neuropsychopharmacol. 2015;25(12):2210-20.

4:00-5:00 ***TMS and Brain Functions*.** Chair: José Rubén García Montes.

Basics and functional effects of transcranial electrical stimulation (tES). Michael A. Nitsche. Leibniz Research Centre for Working Environment and Human Factors, Dept. Psychology & Neurosciences, Dortmund, Germany. University Medical Hospital Bergmannsheil, Dept. Neurology, Bochum, Germany. Neuroplasticity, and functional connectivity are important physiological derivates of cognition, and behaviour. Recently introduced non-invasive brain stimulation techniques are suited to induce, and modulate respective physiological alterations. One of these techniques is transcranial direct current stimulation (tDCS). Its primary mechanism of action is a polarity-dependent subthreshold shift of resting membrane potentials, the after-effects of stimulation depend on the glutamatergic system. Beyond these regional effects, tDCS has been shown recently to alter cortical, as well as cortico-subcortical functional network connectivity. This talk will give an overview about the physiological effects, and will cover functional effects of tDCS on cognitive, emotional and behavioural processes in healthy humans and patients suffering from neuropsychiatric dieases. Finally, it will be shown how alterations of functional oscillatory connectivity via transcranial alternating current stimulation can modify cognitive performance.

Exploring brain functions: TMS-EEG co-registration. Paolo Maria Rossini – Riccardo Di Iorio. Catholic University of Sacred Heart, Policlinico Gemelli Foundation, Rome, Italy. Transcranial magnetic stimulation (TMS) is a painless procedure that involves a short strong electrical current that is delivered through an insulated coil of wire placed over the scalp (magnetic coil). By delivering trains of TMS (repetitive TMS), it is possible to increase or decrease the excitability of cerebral cortex under the stimulating coil depending on the stimulation frequency. When rTMS is applied on cortex areas working as nodes of specific brain networks, it is possible modify the functional activity of the whole network, as observed in experimental setting with different cognitive or motor tasks. The combination of transcranial magnetic stimulation (TMS) and electroencephalography (EEG) is a noninvasive tool to measure the electrical brain reaction to direct cortical stimulation. A single TMS-pulse produces deflections in scalp EEG signals, starting a few milliseconds after the stimulus and lasting about 300 ms, first in the form of rapid oscillations and then as lower-frequency waves (TMS-evoked EEG potentials –TEPs). The co-registration of EEG activity, which has a temporal resolution of a few milliseconds and can be simultaneously sampled from a large number of scalp site, during TMS provides unique possibility to study and probe: brain's excitability, time-resolved functional connectivity, and instantaneous state of the brain. Besides assessment of the general state of the brain, concurrent TMS and EEG have the potential to offer insights into how brain areas interact during sensory processing, cognition or motor control. Several recent findings open up promising possibilities to use this technique to assess directly whether and where in the cortex LTP or LTD plasticity phenomena can be induced with several different paradigms. Detection of the natural frequencies of TEPs with TMS–EEG may also have diagnostic potential and clinical applications, as it opens up possibilities to map the natural frequency of different cortical areas in various neuropsychiatric conditions such as depression, schizophrenia, epilepsy, dementia or disorders of consciousness.

TMS to face dyskinesias in Parkinson's disease. René Drucker-Colín, Jose-Ruben Garcia-Montes. Departamento de Neuropatología Molecular, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México. Ciudad de México. Parkinson's Disease which is a neurodegenerative and progressive disease, results from the degeneration of the Dopamine producing cells originating in the Substancia Nigra pars compacta (SNC) in the Brain Stem. Since the landmark publication of Cotzias

(1967) showing that l-Dopa pharmacological treatment significantly reduced the symptoms of the disease, in time this dose of this medication has to be increased inducing in the patients dyskinesias which are probably more incapacitating than the disease itself. Several investigators have addressed this question and have actively produced several strategies to deal with the dyskinesia problem. However, the problem persists and no complete solution has been found. In this study we have used the technique of rTMS in rats which have been lesioned with 6-OHDA on one SNC, procedure which has been used as the murine model for PD. In due time these rats were administered l-Dopa at a dose of 8 mg/kg for 8 weeks, following which they were given a dose of 12 mg/kg for another 8 weeks. These rats developed evident dyskinesias which were classified according to the Cenci et al scale (1998). Having established the levels of dyskinesias in the rats they were administered sessions of 4 hours daily of TMS. In the following 3 weeks their dyskinesias levels were evaluated. It was found that most rats had either very small intensity dyskinesias or none at all. If TMS was discontinued, the dyskinesias returned and new sessions had to be given. The results therefore showed that TMS could be a good strategy for dealing with dyskinesias, but their administration has to be repeated. Since TMS is a non-invasive procedure, it could be easily administered. It remains to be seen whether with TMS a reduction in l-Dopa could be added, particularly since TMS also has beneficial effects on akinesia.

5:00-6:00 ***Stress and Behavior.*** Chair: Samina Salim.

Glutathione as a glutamate reservoir: The GLU that binds inflammation and neurotransmission. Sedlak, Thomas W.; Koga, Minori; Sawa, Akira. Johns Hopkins School of Medicine, Department of Psychiatry and Behavioral Sciences. Glutamate is the most abundant excitatory neurotransmitter, present at the bulk of cortical synapses, and participating in many physiologic and pathologic processes ranging from learning and memory to stroke. The tripeptide, glutathione, is one third glutamate and present at millimolar brain intracellular concentrations, contributing to anti-oxidant and anti-inflammatory defense. Because of the substantial amounts of brain glutathione and its rapid turnover, we hypothesized that glutathione is a relevant reservoir of glutamate, and could influence synaptic excitability. We find that diminishing the liberation of glutamate by the glutathione cycle produces decreases in cytosolic glutamate, decreased frequency of miniature excitatory post synaptic potentials (mEPSC), and diminished depolarization-associated calcium flux. In contrast, pharmacologically decreasing the biosynthesis of glutathione leads to increases in cytosolic glutamate, increased frequency of mEPSC, and increased depolarization-associated calcium release. The glutathione cycle can compensate for decreased excitatory neurotransmission when the glutamate-glutamine shuttle is inhibited. Glutathione may be a physiologic reservoir of glutamate neurotransmitter that bridges anti-inflammatory pathways and glutamatergic functioning.

A natural product as a tool to explore therapeutic targets for stress-induced microglial immune changes and depressive behaviors. Kamiya, Atsushi. There are a number of clinically effective treatments for stress-associated mental disorders, such as depression. Nonetheless, a large portion of those afflicted exhibit treatment-resistance to first-line treatments, which calls for novel interventions based on pathological mechanisms. Alterations in immune and inflammation processes, including changes in expression of pro- and anti-inflammatory cytokines are observed in patients with depression. Notably, many natural products used in traditional Eastern medicine have been shown to have immunomodulatory properties. In fact, traditional Eastern medicine has been empirically used for treatment of depressive symptom over the past centuries. Nonetheless, there is almost no mechanism-based evidence for the effectiveness of traditional herbal medicines in the treatment of depression. Thus, natural products may be useful tools to uncover novel therapeutic targets of depression by deciphering their mechanisms utilizing modern neuroscience approaches. In this talk, I will present our studies to explore the antidepressant effect of pachyman, a polysaccharide extracted from Poria cocos used as a main ingredient in many traditional Eastern medicines. We examine the effects of pachyman on stress-induced immune changes and depressive behaviors to define its mechanisms of action, which may provide a basis for identifying novel drug targets for the prevention and treatment of depression and related mental conditions.

Oxidative Stress and Psychological Stress: A Cause or Consequence? Samina Salim1 and Naimesh Solanki1. 1Department of Pharmacological & Pharmaceutical Sciences, College of Pharmacy, University of Houston. The brain is a target of stressful and often traumatic experiences. Therefore, recovering from stressful experiences is crucial for normal brain function. In fact, persistent psychological stress often disrupts recovery or adaptive mechanisms causing cognitive and emotional disturbances. It is well recognized that stress adaptation is an integration of a highly complex multi-systemic response mechanism yet, the biochemical determinants of stress response are not known. We have employed numerous behavioral and pharmacological approaches to examine role of oxidative stress in stress-recovery processes. Defective oxidative/antioxidative balance seems to be a critical component of maladaptive stress responsiveness in rodents. Our work has suggested that induction of various forms of psychological stress including social defeat, sleep deprivation, single-prolonged stress, traumatic events, all lead to behavioral and cognitive deficits in rats, along with an increase in oxidative stress markers in the periphery as well as in selected regions of the brain including the hippocampus, amygdala and the prefrontal cortex. Heightened oxidative stress was found to be associated with decreased levels of antioxidant enzymes including Cu/Zn superoxide dismutase (SOD), Mn-SOD, glutathione reductase-1, glyoxalase-1. And, pharmacological strategies to limit oxidative stress replenished antioxidant pool and rescued or prevented some of the behavioral and cognitive deficits observed in a rat social defeat model. These data suggest that critical examination of oxidative stress pathways in animal models of psychological stress might reveal molecular targets critical for development of therapeutic interventions. Funding: NIMH (2R15MH093918-02).

The Role of Inflammation in PTSD and its Modulation by COMTVal158Met Genotype. Victoria Risbrough1,2, Jessica Deslauriers2, Caroline Nievergelt1,2, Dewleen Baker1,2, Mark Geyer2. Center of Excellence for Stress and Mental Health, San Diego Veteran Affairs Health Services, Department of Psychiatry, University of California San Diego. Posttraumtic stress disorder (PTSD) has a lifetime prevalence of 6%, while the lifetime prevalence for experiencing a significant traumatic event is >90%. Understanding the biological mechanisms for why some individuals develop PTSD after trauma while others do not is critical for the development of novel treatment approaches. The role of inflammation and the pathways that control immune responses are coming under increasing scrutiny for their potential role in PTSD risk and symptom development. Here we will briefly review our work from the Marine Resiliency Study and from others in identifying peripheral markers of inflammation that are associated with increased risk for developing PTSD, showing that differences in innate immune function as measured by gene expression patterns, reductions in vagal signaling as measured by heart rate variability and increases in C-reactive protein are linked to increased risk for PTSD. We will also show new analyses from our prospective, longitudinal study of PTSD risk in Active Duty Marines examining how trauma and a functional variant in the gene for the catecholamine degradation enzyme, catechol-o-methyltransferase (COMT; COMTVal158Met), may modulate both PTSD symptoms and inflammatory markers in Active Duty Marines after combat deployment. We will also present data describing similar robust differences in PTSD-like behaviors and peripheral and central markers of inflammation in mice humanized for the COMTVal158Met variants that undergo the predator stress model of PTSD. Finally we will discuss future mechanistic studies in understanding how COMTVal158Met polymorphism may alter inflammatory and stress responses to modify PTSD risk.

5:00-6:00 ***Pharmacological manipulation of trace amine-associated Receptor 1 signaling challenges conventional concepts of psychostimulant action.*** Chair: David Grandy; Co-Chair: Raul Gainetdinov.

Behavioral Consequences of Modulating Glutamate Transmission by TAAR1. Gainetdinov R.R.1,2. 1Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, 199034, Russia; 2Skolkovo Institute of Science and Technology (Skoltech), Skolkovo, Moscow, Russia. G protein-coupled Trace Amine-Associated Receptor 1 (TAAR1) is emerging as a promising new target for psychiatric disorders. Recent progress in identifying selective ligands for TAAR1 led to the possibility of evaluation of the functional consequences of stimulation/ blockade of TAAR1. By using these compounds in an

experimental paradigm developed in our laboratory that involves dopamine transporter knockout mice, a novel model of acute dopamine deficiency, and mice lacking TAAR1 (TAAR1-KO mice), we explored the role of TAAR1 in modulation of dopaminergic and glutamatergic transmission. Pharmacological or genetic targeting of TAAR1 revealed that stimulation of TAAR1 suppressed dopamine-dependent behaviors, while TAAR1 deficiency potentiated them. TAAR1-selective ligands have shown potential antipsychotic, antidepressant, and pro-cognitive effects in experimental animal models; however, it remains unclear whether TAAR1 can affect PFC-related processes and functions. Recently, we documented a distinct pattern of expression of TAAR1 in the PFC, as well as altered subunit composition and deficient functionality of the glutamate N-methyl-D-aspartate (NMDA) receptors in the pyramidal neurons of layer V of PFC in mice lacking TAAR1. The dysregulated cortical glutamate transmission in TAAR1-KO mice was associated with aberrant behaviors in several tests, indicating a perseverative and impulsive phenotype of mutants. Conversely, pharmacological activation of TAAR1 with selective agonists reduced premature impulsive responses observed in the fixed-interval conditioning schedule in normal mice. This study indicates that TAAR1 plays an important role in the modulation of NMDA receptor-mediated glutamate transmission in the PFC and related functions. Furthermore, these data suggest that the development of TAAR1-based drugs could provide a novel therapeutic approach for the treatment of disorders related to aberrant cortical functions. This work was supported by the Russian Science Foundation (project 14-50-00069).

TAAR1 activation reduces cocaine intake and relapse: behavioral and neurobiological evidence. Jun-Xu Li 1. 1 Department of Pharmacology and Toxicology, University at Buffalo, the State University of New York. Trace amine-associated receptor 1 (TAAR 1) is a recently described G-protein coupling receptor that is expressed both centrally and peripherally. In the central nervous system, a substantial co-expression exists on TAAR 1 and dopamine transporters. Studies using TAAR 1 knockout mice suggest that TAAR 1 knockout increases the sensitivity of animals on their response to psychostimulants. Electrophysiological and neurochemical studies also suggest the role of TAAR 1 in modulating central dopaminergic activity. This study examined the effects of a TAAR 1 partial agonist RO5263397 on the reinforcing effects of cocaine using behavioral economic analysis and also examined the effects of a TAAR 1 full agonist RO5166017 on environmental cue- and drug-induced reinstatement of cocaine-seeking behavior in rats self-administering cocaine. Cocaine maintained a stable self-administration behavior and RO5263397 significantly increased the plasticity of the demand curve, suggesting reduced reinforcing effectiveness of cocaine when RO5263397 was present. After the lever-pressing behavior was extinguished when cocaine was unavailable, both environmental cue and cocaine priming injection significantly reinstated the extinguished lever-pressing behavior. RO5166017 significantly reduced both cue- and cocaine prime-induced reinstatement of cocaine-seeking. Microinjection of RO5166017 into different brain regions (ventral tegmental area, prelimbic and infralimic cortex, nucleus acuumbens shell and core, and substantia niagria) differentially modulated cue- and cocaine prime-induced reinstatement. Together, these results suggested that TAAR 1 activation reduces the reinforcing effectiveness and cocaine relapse due to environmental cue and drug priming, which seems to be mediated via different brain regions. Studies are supported by NIH grant DA033426.

Modulation of mouse behavior and cognition by the endogenous TAAR1 agonist 3-iodothyronamine. Riccardo Zucchi. University of Pisa, Italy. 3-iodothyronamine (T1AM) is an endogenous amine detected in mouse brain at nanomolar concentration. It is probably derived from thyroid hormone through decarboxylation and deiodination. In vitro experiments showed that T1AM is a high affinity agonist of trace amine-associated receptor 1 (TAAR1), although it can also interact with TAAR5 and with adrenergic receptors. Administration of exogenous T1AM in mouse cerebral ventricles modulated food assumption in a biphasic way, reduced pain threshold in the hot plate test, increased curiosity in the object recognition test, and elicited a pro-learning and anti-amnestic effect in the passive avoidance test. Pharmacological experiments showed that these effects are mediated at least in part by interference with other aminergic systems, particularly the histaminergic system. In mouse entorhinal cortex, long-term potentiation (LTP), that is believed to be one of the basic mechanisms of memory, was inhibited by the specific TAAR1 agonist EPPTB and was reduced in TAAR1 knock out animals vs wild

type littermates. In entorhinal cortex slices, LTP was abolished by exposure to the toxic fragment of beta amyloid, and it was rescued by T1AM administration. The latter effect was removed by EPPTB. T1AM also rescued LTP in the entorhinal cortex obtained from a transgenic mouse model of Alzheimer disease. Western blot experiments confirmed that TAAR1 is expressed in the entorhinal cortex. In conclusion, T1AM and TAAR1 might pay a significant physiological and/or pathophysiological role in the central nervous system.

6:30-8:30 **Poster Session 1.**

1. **The interaction of oxytocin and the vasopressin V1A receptor in reducing relapse to methamphetamine abuse.** Everett, N.A., Baracz, S.J., Cornish, J.L. Macquarie University, NSW, Australia. Methamphetamine (METH) is a highly addictive psychostimulant. Currently there are no approved pharmacotherapies for METH dependence, although animal models of drug abuse have highlighted the therapeutic potential of the neuropeptide oxytocin in treating addiction to METH. The nucleus accumbens core (NAcc), an important brain region for addiction and relapse, has been identified as an important site for oxytocin-METH interactions. However, the inhibitory effects of oxytocin administration on relapse to METH-seeking behaviour does not appear to be mediated by the oxytocin receptor (OTR) within the NAcc, and further, it has not yet been shown if the effect of systemic administration of oxytocin to reduce METHseeking behaviour is mediated by the OTR. The structurally similar vasopressin V1A receptor (V1AR) has been located within the NAcc, has been implicated in numerous oxytocin-driven social behaviours, and is readily activated by oxytocin. Therefore, using the intravenous drug self-administration mode of reinstatement, we investigated a role for the V1AR in mediating the attenuating effects of oxytocin on METH-related behaviours, when administered systemically, and when microinjected into the NAcc. 32 male Sprague-Dawley rats were surgically implanted with intravenous jugular vein catheters, with half also receiving bilateral intracranial cannulae into the NAcc. After recovering from surgery, rats were trained to self-administer METH by lever pressing during daily 2-hr fixed ratio 1 scheduled sessions for 20 days. Following extinction of a preference for the active lever, rats were tested for the effects of oxytocin alone, and when co-administered with the V1AR antagonist SR49059 on METH-primed reinstatement of METH-seeking behaviours, when administered systemically, or when microinjected into the NAcc. This study is the first to demonstrate an important role for the V1AR in mediating the inhibitory effects of oxytocin on METH-related behaviours, and has important implications for the development and discovery of novel oxytocin-based pharmacotherapies for METH dependence.

2. **Single-Exposure Conditioned Place Preference: An animal model of initial subjective drug effects.** Judith Grisel. Bucknell University, Lewisburg PA 17837, USA. Despite urgent need and ample effort, the neural and behavioral predisposition for drug addiction remains poorly understood. This is due partly to the complex set of interacting risk factors (i.e., genetic, developmental and other environmental contributions) but progress has also been hampered by a paucity of animal models for investigating predisposition. We recently developed a model of initial-subjective reward to alcohol in mice, employing a single exposure conditioned place preference (SE-CPP) procedure to identify factors contributing to individual susceptibility to the drug (Grisel et al., 2014). Two conditioning sessions (one immediately following drug injection, the other after saline) during which rodents experience two different floor textures, are followed by a test where subjects are free to explore either conditioning environment or a neutral center zone. Conditioning takes place on Day 1 and 3, and testing on Day 5, while animals are left undisturbed in their home cages on Days 2 & 4. We've extended our initial findings in mice to rats and additional drugs (morphine and diazepam). We think these studies can help to generate a better understanding of addiction liability by elucidating some of the genetic, neurochemical and environmental factors that contribute to initial sensitivity to a drug's reinforcing properties, an important endophenotype in the trajectory toward excessive use (Ray et al, 2016 for a recent review). For instance, our results suggest that endogenous opioids play a critical role in the initial subjective reward to alcohol, and also suggest that negative reinforcement mediates reward from sedative-hypnotic drugs. We've also shown that exposure to the drug-paired context can be very brief (e.g., 5 min) making the SE-CPP a high-

throughput assay relative to other measures of drug reinforcement. We think this model will be generally useful to basic researchers interested in studying the neural substrates of addiction and help furnish a foundation for improved interventions and treatments.

3. **Is there an implicit association between physical activity and alcohol consumption?** Najjar, Laian Z.1; Neighbors, Clayton2; Henderson, Craig E.3; Young, Chelsie M.4; Hoyt, Alex5; Leasure, Jennifer L.6 1, 2, 4, 5, 6 University of Houston, Department of Psychology, Houston, TX, USA, 3Sam Houston State University, Department of Psychology, Houston, TX, USA. Physical activity has been suggested as a potential intervention for alcohol use disorders (AUD), however, there is conflicting evidence as to its efficacy. This may be due, in part, to the well-established positive relationship between physical activity and alcohol intake, in that drinkers tend to be more active than non-drinkers. Prior studies have focused mainly on the explicit relationship between physical activity and alcohol consumption; however, examining a potential implicit link between alcohol use and exercise may help clarify the nature of the relationship. The overarching objective of this study was to determine whether there is an implicit association between physical activity and alcohol consumption. A second objective included evaluating potential joint motives for exercise and drinking, as that may further clarify the alcohol consumption-physical activity relationship. Male and female participants (N=391; 77% female) aged eighteen and above were recruited from two large southwestern universities. Participants completed self-report measures of alcohol frequency and quantity, drinking motives and enjoyment, exercise frequency and intensity, exercise motives and enjoyment, and religious perceptions pertaining to alcohol consumption. To evaluate implicit attitudes, participants took three Implicit Association Tests (IATs). IAT1 tested implicit attitudes toward alcohol consumption and exercise, with targets alcohol/water and attributes exercise/inactivity. IAT2 evaluated implicit drinking identity attitudes, with targets drinker/non-drinker and attributes me/not me. IAT3 examined implicit attitudes towards exercise importance, with targets exercise/rest and attributes important/unimportant. We expected to find a stronger implicit association between exercise and alcohol intake in participants who drink more in quantity and frequency, and those who exercise more intensely and frequently; we also expected the implicit link to be strongest in those who enjoy doing both. Additionally, we hypothesized that individuals motivated to drink will have a stronger implicit drinking identity; and individuals with joint motives for exercise and drinking will have a stronger implicit association between both, and will drink and exercise more. Contrary to our central hypothesis, our results yielded no association between implicit attitudes toward physical activity and alcohol use and actual behaviors for both. However, we did find that participants motivated to drink have a stronger implicit drinking identity, and those who expressed joint motivation to exercise and drink have a stronger implicit association between exercise and drinking, and tend to drink more. Taken together, these findings provide preliminary evidence that link implicit attitudes, joint motives for physical activity and alcohol use, and the behaviors of exercise and drinking. Having a better understanding of these relationships may help in the development of more effective exercise-based interventions.

4. **Chronic Alcohol Drinking Alters Modulation of Dopamine Release in Rhesus Monkey Dorsal Striatum.** David M. Lovinger1, Armando Salinas1, Verginia Cuzon Carlson2, Yolanda Mateo1, Kathleen A. Grant2. 1National Institute on Alcohol Abuse and Alcoholism, 2Oregon National Primate Research Center. The dorsal striatum (DS) has key roles in the neural actions of drugs of abuse, and in drug taking. As part of a large program examining effects of prolonged alcohol drinking in Macaca mulatta, we have used fast-scan cyclic voltammetry to measure electrical stimulus-induced dopamine release in the caudate and putamen DS subregions. Dopamine release was decreased in both DS subregions in slices from male monkeys that drank alcohol in comparison to controls. Surprisingly, dopamine release was increased in caudate slices from female monkeys. We applied the dopamine D2 receptor agonist quinpirole to assess the efficacy of modulation by presynaptic receptors. Quinpirole suppression of dopamine release was reduced in slices from alcohol drinking male, but not female, caudate and putamen in comparison to controls. It is now clear that striatal dopamine release can be driven by activation of cholinergic interneurons and subsequent activation of nicotinic acetylcholine receptors on dopaminergic terminals. This mechanism is engaged when electrical stimulation is given in striatal slices.

Indeed, we observed that nicotinic receptor blockade with dihydro-beta-erythroidine (DHBetaE) reduces stimulus-induced dopamine release in both caudate and putamen monkey slices. This antagonist effect was reduced in chronic drinking male putamen relative to controls, and indeed nicotinic receptor blockade enhanced dopamine release induced by brief higher frequency stimulus bursts only in putamen slices from alcohol-drinking monkeys. These findings indicate that prolonged alcohol consumption alters dopamine release and feedback control of release in both striatal subregions. Altered cholinergic control of release is observed in the putamen following prolonged drinking. Different adaptations in male versus female striatum will be discussed in relation to sex differences in drinking pattern.

5. **Sex differences in the effects of naltrexone on appetitive and consummatory responses to ethanol in adult rats.** Steven J. Nieto1, Kevin J. Winoske1, & Therese A. Kosten1. 1Department of Psychology, University of Houston, Houston, TX, United States. A wealth of animal studies provide support for the use of the mu-opioid antagonist, naltrexone, for the treatment of alcohol use disorders (AUDs). Although clinical studies show efficacy of naltrexone for AUDs, the data on whether it is differentially effective in males and females is mixed. Moreover, there are sex and gender differences in mu-opioid system that suggest naltrexone may alter alcohol self-administration differentially by sex in animals. The present study tested whether sex differences exist in the ability of naltrexone to decrease consummatory (e.g., numbers of reinforcers delivered) and appetitive behaviors (e.g., head entries into the dipper area) in an operant alcohol self-administration paradigm. Separate groups of male and female Sprague Dawley rats (n's=611) were trained to lever press for either ethanol (10%; EtOH) or sucrose (3%; SUC) in standard operant chambers under a fixed ratio 2 (FR2) schedule of reinforcement. The effects of a broad range of naltrexone doses (0, 0.1, 0.3, 1, 3, & 10 mg/kg) were assessed in tests conducted under a progressive ratio schedule of reinforcement. In males, naltrexone administration led to dose related decreases in both appetitive and consummatory behaviors in the EtOH group, but not in the SUC group. Naltrexone was more efficacious for appetitive vs. consummatory behaviors. For example, numbers of active lever presses were significantly decreased at doses of 1 mg/kg and higher whereas consummatory behaviors were significantly reduced only at the 10 mg/kg in the EtOH group. Naltrexone administration did not significantly alter these behaviors in the female EtOH or SUC group. Together, our findings suggest that naltrexone decreases appetitive and consummatory behaviors for alcohol only in male rodents. These findings highlight the need for further investigations assessing the effectiveness of pharmacological treatments for alcohol use disorders in both genders. This work was supported by NIAAA U01AA013476.

6. **Context-independent effects of footshock on drug-seeking.** Christie Pizzimenti1, Thomas Navis1, K. Matthew Lattal1. 1Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, OR. 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 examined the effects of massive footshock in one context on cue-induced drug-seeking for methamphetamine in another context. In Experiment 1, animals were trained to self-administer methamphetamine in Context A. On day 8 of self-administration (16 total sessions) animals received either a battery of footshocks in Context B or exposure to that context only, and were then allowed to continue daily self-administration sessions in Context A. Animals that received shock reinstated significantly more than controls to drug-associated cues and took significantly longer to extinguish lever pressing following reinstatement. In Experiment 2 the battery of footshocks were administered in Context B before acquisition of self-administration in Context A. Animals that received footshock showed significantly elevated responding during cue-induced reinstatement. In a separate group of animals, the battery of footshocks was also shown to significantly elevate plasma levels of corticosterone relative to exposure only controls to levels that are consistent with physiological stress. Taken together, these results suggest that this novel, translatable model replicates the human condition in which exposure to a massive stressor in a specific context produces long-term changes in drug-

seeking behavior in non-fear associated contexts. This is evidenced by significantly elevated reinstatement to drug-related cues and resistance to extinction following reinstatement.

7. **The role of behavioral contingency in excessive cocaine-induced escalation of intake.** Ploense, Kyle; Vieira, Philip; Bubalo, Lana; Olivarria, Gema; Carr, Amanda; Kippin, Tod. Cocaine addiction is a chronic disorder that involves excessive, uncontrolled drug consumption. Both humans and rodents will escalate the amount of cocaine taken when it is readily available indicating that excessive intake is dependent on prior consumption. In rodents, however, escalation is not observed when access is restricted to "limited" (i.e. 1 hr) daily sessions. Here, we investigated whether control over drug intake or drug exposure are the critical factors in escalation by employing a mixed limited-contingent exposure and prolonged noncontingent exposure model. . Rats were implanted with a permanent jugular catheter and then allowed to lever press to self-administer (FI20 with a 20 s light cue paired with each infusion) saline vehicle (0.1 ml/infusion) or cocaine (0.25 mg/infusion) under 3 conditions: limited-access (1 h/ day), extended-access (6 h/day), and 1 h limited-access + 5 h non-contingent exposure (via yoking to extended access rats) to cocaine. Based on the first 10 min and first hour of daily access, we observed rapid escalation of cocaine intake in both the extended-access and limited-access + non-contingent conditions ($ps < 0.05$). We also observed a delayed escalation of cocaine intake in the limited-access condition within the first 10 min of self-administration ($p < 0.05$), but not across the 1 h of cocaine availability. Interestingly, escalation of cocaine intake was accelerated in the limited + non-contingent-access condition relative to the extended-access condition. However, relative to the other cocaine conditions, the limited-access + non-contingent group exhibited markedly more non-reinforced responses indicating that distinct behavioral mechanisms drive escalation by contingent versus noncontingent drug exposure ($ps<0.05$). Additionally, post-mortem quantification of homer2 (a gene implicated in cocaine intake and associated) mRNA expression within the dmPFC indicated elevation only in the extended-access conditions ($p<0.05$). Rises in homer2 mRNA were associated with distinct levels of DNA methylation, hydroxymethylation, and transcription factor binding to the Homer2 gene. Together, these findings indicate that either contingent or non-contingent "excessive" cocaine exposure supports escalation but have differential effects on the temporal patterning of operant responsiveness as well as molecular correlates of escalation.

8. **Prenatal testosterone activity determines adult alcohol drinking and morphology in male and female mice.** Sabine E. Huber, Bernd Lenz, Johannes Kornhuber, Christian P. Müller. Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany. An accepted marker for prenatal sex hormone exposure is the second-to-fourth-digit ratio (2D:4D). It was shown that the 2D:4D ratio can be altered in mice by modification of the prenatal hormonal balance. Moreover a recent study demonstrated that alcohol-dependent patients exhibited reduced 2D:4D ratio. This suggests that prenatal sex hormones might influence the development of alcohol addiction. The aim of our study was to investigate the role of prenatal dihydrotestosterone (DHT) and flutamide (an androgen receptor antagonist) administration on alcohol addiction and mouse morphology. Prenatally treated offspring of CD1 dam mice were tested in a two-bottle choice paradigm with increasing alcohol concentrations (2 – 16 vol%). Following the test for addictive behavior was a taste preference test, with either a sweet (0.5 and 5% sucrose) or a bitter (2 and 20 mg quinine) solution. The 2D:4D ratio was analyzed using GIMP software on scans of the paws and head size, body and tail length were measured. Prenatal androgen receptor inhibition by flutamide led to a decrease in alcohol consumption, preference and total fluid intake in males, as well as to a reduced alcohol preference, but increased water consumption, in females. Prenatal activation of the androgen receptor by DHT, in females, increased alcohol drinking and preference, while in males it enhanced the water and total fluid intake. In females, all receptor modification groups showed an increased total fluid intake. No differences between treatments and sex could be detected in the preference of sweet taste or avoidance of bitter taste. Androgen receptor activation led to a higher 2D:4D ratio in male hind paws (left and right paw taken together), while in females a reduced 2D:4D ratio in hind paws could be observed following prenatal receptor inhibition. Prenatal treatment with flutamide increased head size and body length in males, in

females, however, it decreased tail length. Decreased body and tail length could be measured in females treated with prenatal DHT. In conclusion, we could show that prenatal androgen receptor activation is required for the full expression of adult alcohol drinking behavior in mice. Furthermore we found a double dissociation in the role of prenatal androgen receptor activity for adult alcohol vs. water drinking motivation in males and females.

9. **Prenatal alcohol exposure alters cranially directed blood flow and neurological responses to transient cerebral ischemia in adult mice.** Bake, Shameena; Gardner, Rachel; Tingling, Joseph; Miranda, Rajesh C; Sohrabji, Farida. Texas A&M Health Science Ctr. Prenatal alcohol exposure can result in a collection of craniofacial, growth and neurocognitive deficits that are collectively termed 'Fetal Alcohol Spectrum Disorders' or FASD. FASD is the leading cause of neurodevelopmental disability worldwide. Though FASD is recognized as a source of life-long disability, and a cause for the emergence of secondary disabilities, the mechanisms underlying the emergence of secondary disability have been poorly studied. Based on our previous data showing that maternal ethanol exposure in mice resulted in an immediate reduction in cranially directed fetal blood flow, we hypothesized that such exposure would also result in persistent alterations in cranially directed blood flow in the FASD adult as well. We also hypothesized that FASD adults exposed to a new cerebrovascular insult would exhibit more brain damage and neurobehavioral impairment compared to non-FASD adult controls. To test the above hypotheses, pregnant mice were exposed to ethanol, 3g/kg, or water by intra-gastric gavage. Blood flow in carotid, renal and femoral arteries was assessed by ultrasound imaging in FASD and control adults, at 3, 6 and 12 months of age. The middle cerebral artery was transiently occluded (MCAo) in FASD and control animals at 3 months of age, to mimic ischemic stroke in young adult populations. Our data show that prenatal ethanol exposure resulted in a significant decrease in blood acceleration in the carotid but not renal and femoral artery at 6 and 12 months of age. A unilateral MCAo resulted in equivalent cortico-striatal damage in both FASD and control adults. However, FASD adult mice exhibited significantly decreased post-stroke behavioral recovery compared to controls. Our data collectively show that FASD adult mice exhibit a persistent, long-term loss of cranially directed blood flow, and decreased capacity to compensate for a second episode of neural injury in adulthood. Supported by R01AG042189 (FS), R01NS074895 (FS), R01AA013440 (RCM) and the Texas A&M Chou award (SB).

10. **Magnetic field stimulation diminishes the probability to increase dyskinesia and decreases FosB in the genetic and 6-OHDA models of Parkinson´s disease.** García-Montes José-Rubén12, Ruiz de Diego Irene12, Solís-Castrejón Oscar12, Drucker-Colín René34, Moratalla Rosario12. 1 Instituto Cajal, Consejo Superior de Investigaciones Cientı´ficas, CSIC, Madrid, Spain. 2 CIBERNED, ISCIII, Madrid, Spain. 3 Instituto de fisiología Celular, Universidad Nacional Autónoma de México, Ciudad de México, México. 4Secretaría de Ciencia Tecnología e Innovación de la ciudad de México. The development of non invasive therapies to treat neurological disorders is allowing the possibility to avoid side effects of drugs; Dyskinesia is an undesired side effect of Levodopa (L-DOPA) which has been the main challenge since Birkmayer and Cotzias established this therapy for Parkinson´s disease (PD) in 60´s. Many pharmacological strategies have tried to decrease the occurrence of dyskinesias by taking advantage of pharmacology. On the other hand non invasive therapies like exposure to magnetic fields have been poorly studied. The aim of this study is to test the effects of Extremely Low Frequency Magnetic Field exposition (ELFMF) on two mouse models of PD. To achieve this we tested the effect of 200 kA m-1 at 50 Hz restricted to the head during 2hrs daily in both models, 6-OHDA and Aphakia mice (Pitx3 KO). The experiment was divided in two segments, first segment portends to analyze the effect of magnetic field exposure on the bilateral and genetic mice model of PD and the second segment to analyze the hemiparkinsonian model lesioned with 6-OHDA. Aphakia mice were divided in two groups, the group without exposition to magnetic field (Aph) and the group exposed to magnetic field (Aph+ELFMFS). To test the hemiparkinsonian we divided lesioned mice in two groups, the group without exposition to magnetic field (6-OHDA) and the group exposed to magnetic field (6-OHDA+ELFMFS). After Basal measurements, motor behavior and dyskinesias of both groups in both segments were qualified by a blind researcher. After 15 days of L-DOPA treatment 10mg Kg-1 mice were sacrificed and the brains were

sliced and stained using FosB antibodies, an early gene over expressed in dyskinesia. Results with the Aphakia experiment showed no statistically significant change when compared total activity, horizontal activity and vertical activity of the Aph group versus Aph+ELFMFS group. The analysis of the blind researcher reveals no differences of 4 paw dyskinesias when compare treated vs non treated Aphakia mice. On the other hand the results of 6-OHDA experiment reveals a significant increase of 2 points on total dyskinesia score ($p=0.03$) on day 40 of L-DOPA treatment comparing versus day 22 in the 6-OHDA group. Results also demonstrate no significant difference before and after the ELFMFS in the 6-OHDA+ELFMFS group and finally no changes were observed comparing 6-OHDA versus 6-OHDA+ELFMFS group at the end of the experiment. Strikingly, the results of count reactive nuclei to FosB in both 6-OHDA and Aph mice showed a significant decrease of FosB expression in denervated zone by ELFMFS treatment ($p<0.001$ and $p<0.01$ respectively). In summary, our study showed that ELFMFS could be a strategy to avoid the increase of dyskinesia. Finally the evident effect in molecular markers of dyskinesia is a good read out of the strong effect this therapy might represent.

11. **Behavioral and molecular-biological characterization of a new rat substrain: relevance to neuropsychiatric disorders.** Kekesi G.1, Ducza E.2, Büki A.1, Benedek G.1, Horvath G1. 1Department of Physiology, Faculty of Medicine, 2Institute of Pharmacodynamics and Biopharmacy, Faculty of Pharmacy, University of Szeged, Szeged, Hungary. Background: Selective breeding of rats after postweaning social isolation and subchronic ketamine treatment lead to behavioral changes related to neuropsychiatric disorders, i.e. shizophrenia and/or autism. Since both schizophrenic and autistic patients often suffer from impairments in working memory, and brain-derived neurotrophic factor (BDNF) and glutamate decardboxylase gene 1 (encoding GAD67) mRNA levels have been shown to be decreased in their dorsolateral prefrontal cortex, it is highly likely that these molecular-biological alterations play some role in the etiology of these neurodevelopmental disorders. The aims of the present study were: 1) the behavioral phenotyping of the new rat substrain (22nd generation) with a multiple test battery and 2) to determine the potential molecular-biological alterations in its background to strengthen the translational validity of our complex model. Methods: To assess acute heat pain sensitivity, sensory gating properties and working memory functions the tail-flick, prepulse inhibition and modified hole-board tests were applied subsequently in male rats beginning at the age of 9 weeks. After the behavioral phenotyping the in vitro reverse transcriptase-polymerase chain reaction (RT-PCR) was used to detect schizophrenia-related mRNA expressions in the prefrontal cortex. Results: Decreased acute heat pain sensitivity, sensory gating disturbances and cognitive impairments were characteristic to the selected rats. RT-PCR studies revealed significantly lower BDNF and GAD1 mRNA expressions in the prefrontal cortex samples of the new substrain compared to control ones. Conclusion: The decreased expression of BDNF and GAD1 mRNA and the behavioral phenotype are similar to that described in schizophrenic patients. These results enhance the constructive validity of our complex animal model and its relevance to use it in translational researches. This work was supported by OTKA (K 83810), TÁMOP-4.2.2.B-15/1KONV-2015-0006.

12. **Effects of systemic administration of ibuprofen on stress response 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, 130-701, Republic of Korea. 2The Graduate School of Basic Science of Korean Medicine, College of Korean Medicine, Kyung Hee University, Seoul, 130-701, Republic of Korea. Pro-inflammatory cytokine and brain-derived neurotrophic factor (BDNF) are modulated in post-traumatic stress disorder (PTSD). This study investigated the effects of ibuprofen (IBU) on enhanced anxiety in a rat model of PTSD induced by a single prolonged stress (SPS) procedure. The effects of IBU on inflammation and BDNF modulation in the hippocampus and the mechanisms underlying these effects were also investigated. Male Sprague-Dawley rats were given IBU (20 or 40 mg/kg, i.p., once daily) for 14 days. Daily IBU (40 mg/kg) administration significantly increased the number and duration of open arm visits in the elevated plus maze (EPM) test, reduced the anxiety index in the EPM test, and increased the time spent in the center of an open field after SPS. IBU administration significantly decreased the

expression of pro-inflammatory mediators, such as tumor necrosis factor-α, interleukin-1β, and BDNF, in the hippocampus, as assessed by reverse transcription-polymerase chain reaction analysis and immunohistochemistry. These findings suggest that IBU exerts a therapeutic effect on PTSD that might be at least partially mediated by alleviation of anxiety symptoms due to its anti-inflammatory activity and BDNF expression in the rat brain.

13. **Gene variants in cytochrome P450 CYP2C19 and CYP2D6 are associated with psychosis in a clinical sample of persons with Down syndrome.** Malt, Eva1,2; Dahl, Renate; Juhasz, Katalin1; Rud, Ellen1; Haugsand, Trine1; Davidsen, Eva1. 1Department of Adult Habilitation, Akershus University Hospital, Lørenskog, Norway, 2Department of Clinical Medicine, Campus Ahus, University of Oslo, Oslo, Norway. Background: The two major cytochrome P450 polymorphisms with respect to variable drug response, are those of CYP2D6 and CYP2C19. The enzymes also have important roles in metabolism of endogenous substances, and accumulating evidence indicates that the polymorphisms can influence brain function and behavior. CYP2D6 is implicated in generation of serotonin and dopamine from trace amines. Low metabolizers display higher impulsivity-related traits and more anxiety proneness that extensive metabolizers. CYP2C19 is expressed in the fetal brain and metabolizes cannabinoid compounds important for migration of GABAergic interneurons to hippocampus. Persons with allelic variants causing high CYP2C19 enzyme activity show more depressive symptoms than subjects carrying a defective variant. Fetal Down syndrome brains show reduced levels of serotonin, dopamine and GABA in the frontal cortex and reduced migration of GABAergic interneurons to hippocampus. Young adults have higher rates of psychosis than others with intellectual disability. Aim: To examine cytochrome P450 polymorphisms in 2D6 and 2C19 in patients with Down syndrome and psychosis. Method: Chart review of cases admitted to a university based neurological/neuropsychiatric out-patient clinic for adults with intellectual disability in the period 2010 - 2015. Results: In total 90 individuals with DS were admitted for behavioral, neurological or psychiatric symptoms. Five (5,5%) were diagnosed with psychosis, and all of them harbored a combination of one or two activating alleles in CYP2C19 (2C19*17) and one or two null alleles associated with reduced or abolished enzyme activity in CYP2D6 (2D6*5, 2D6*4). Pharmacogenetic testing had been performed in about 40% of the referred patients, but none of those tested without psychosis had this special allele combination. Discussion: Studies have shown that the allele frequency of 2C19*17 present at 18-27% in European populations while the allele frequency for a CYP2D6 null allele is about 15-25%, indicating that the combination of an activating CYP2C19*17 and an inactive 2D6 allele should be present in about 2-7% of the population. Our results suggest that this allele combination is associated with proneness to psychosis in persons with Down syndrome. This may be related to impact of trisomy 21 on neurodevelopmental and metabolic processes influenced by CYP2C19 and CYP2D6. The results should be examined in a larger prospective study.

14. **Prenatal exposure to Intuerluekin-6: A translational study examining component behaviors and MRI based metrics associated with ADHD and autism.** Brian D Mills1, Anandakumar Shunmugavel1, Christie Pizzimenti1, Matt Lattal1, Suzanne Mitchell1, Damien Fair1,2. 1 Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, OR. 2 Advanced Imaging Research Center, Oregon Health and Science University, Portland, OR. A number of psychiatric disorders, including attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) have been linked to prenatal risk factors including maternal obesity, stress, and viral infections during pregnancy. These risk factors share a common mechanism, namely elevated inflammatory cytokines. Resting state functional connectivity (rsfc-MRI) is a noninvasive tool that measures correlated spontaneous brain activity and offers the unique ability to study brain dynamics in both humans and rodent models of disease. ADHD and autism have been repeatedly demonstrated to show atypical resting state connectivity patterns in the default mode network. Further, work in our laboratory has shown that elevated prenatal exposure to interleukins, namely interlukin-6 (IL-6), is associated decreased default mode connectivity in infants, a pattern reminiscent of children with developmental disorders. The current work is a translational project that tests whether prenatal IL-6 plays a causal role in mediating behavioral and brain phenotypes associated with ADHD and ASD. To test this, Sprague-Dawley rats were implanted with

osmotic pumps delivering either saline or a daily dose 4.98 ug/kg IL-6 over the course of 40 days. This dose was designed to mimic chronic inflammatory states throughout pregnancy. Each group was mated and offspring were given a battery of behavioral tests and rsfc-MRI imaging both during adolescence (PD25) and adulthood (PD50). The current work will discuss the effects of chronic prenatal exposure to IL-6 on deficits in social behavior, hyperactivity, and anxiety phenotypes. We primarily find that rats who were prenatally exposed to IL-6 show an anxiety phenotype measured by the light dark test, where IL-6 exposed animals spend less time in the light primarily during the first behavioral test at PD25. No differences were found in locomotor activity at either time point and a trend level effect of decreased social preference was also observed. Importantly, aberrant default mode connectivity in IL-6 exposed animals suggests a converging neural phenotype between the effects of early IL-6 exposure and brain connectivity abnormalities seen in children with developmental disabilities. Overall, this work sheds light on the underlying mechanisms associated maternal inflammation and the role of IL-6 as risk factor for developing phenotypes seen in ASD and ADHD.

15. **Neural response to cognitive and emotional empathy task in the brain of autism spectrum disorder.** Jung-Woo Son1, Seungwon Jung1, Lsbok Lee2, Hei-Rhee Ghim2. 1; Department of Neuropsychiatry, College of Medicine, Chungbuk National University, South Korea. 2; Department of Psychology, Chungbuk National University, South Korea. The essential feature of autism spectrum disorder (ASD) is impairment in social interaction. Empathic ability plays a key role in social relationship. Recent evidence supposed that there are two systems for empathy: cognitive and emotional. We purposed to elucidate psychological aspects and brain activity in ASD from the viewpoint of cognitive and emotional empathy. 17 individuals with ASD and 22 age- and sex-matched heathy comparison individuals were scanned with functional magnetic resonance imaging (fMRI) during both cognitive and emotional empathy tasks. Differences in brain activation between two groups were assessed by contrasting neural activation during the tasks. During both cognitive and emotional empathy tasks, ASD subjects showed greater neural activities in the bilateral cuneus (Brodmann area 18)compared to control subjects.And they showed more activationin the bilateral precuneus (Brodmann area 7)only during emotional empathy task. There was no brain region more activated in control subjects during cognitive empathy task. But while carrying out emotional empathy task, control subjects exhibited greater neural activities in the left middle frontal gyrus (Brodmann area 46) and right anterior cingulate gyrus (Brodmann area 32) than ASD subjects. This fMRI study showed the differences in neural activity during the cognitive and emotional empathy tasks between individuals with ASD and healthy control individuals. Further research will be needed to investigate more definite neurobiology of ASD in terms of empathy.

16. **The role of mesopontine cholinergic neurons in prepulse inhibition of startle.** Azzopardi, Erin; Louttit, Andrea; Haddad Faraj; Schmid, Susanne. Department of Anatomy and Cell Biology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada. Prepulse inhibition (PPI) is a pre-attentive process that suppresses sensory evoked motor responses in favor of an orienting response towards a sensory stimulus. It is hypothesized that the mechanism underlying PPI is cholinergic inhibition of startle neurons in the brain stem by cholinergic projections from mesopontine neurons, located in the pedunculopontine tegmental nucleus (PPT) and laterodorsal tegmentum (LDT). To test this, we injected transgenic rats (Chat-Cre) with either a DREADD, optogenetic (ChR2), or respective control virus into the PPT in order to transiently inactivate or activate these neurons and test the effect on startle/PPI. DREADD inhibition of mesopontine cholinergic neurons did not disrupt PPI at different prepulse levels or interstimulus intervals tested, but seems to slightly decrease baseline startle. DREADD induced inhibition did disrupt morphine conditioned place preference (CPP) as a positive control measure. Conversely, optogenetic stimulation of the PPT/LDT did not induce PPI, but rather facilitated startle in the ChR2 expressing rats. This facilitation was most robust at the ISI of 15 ms, and could be blocked by a nicotinic antagonist. Optogentic stimulation also caused CPP in ChR2 transfected rats, but not in control animals, as a positive control. Our results suggest that the cholinergic cells of the PPT may not be as critical for PPI, as generally assumed, but might rather increase startle responses in accordance to their assumed function in arousal.

17. **The Aid of Ephedrine HCL, Curcumin and Turmerone in Neurogenesis and Inhibition of Beta-Amyloid Plaques in Transgenic Mice Models.** Dr.Keerthi Paramasivam. King's College London, WC2R 2LS, United Kingdom. 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.

18. **The therapeutic potential of cannabidiol for Alzheimer's disease.** David Cheng1,2, Andrew Jenner3, Andrea Spiro3, Brett Garner3 and Tim Karl1,2. 1Neuroscience Research Australia, Sydney, NSW, Australia. 2School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia. 3Illawarra Health Medical Research Institute, University of Wollongong, Wollongong, NSW Australia. 4School of Medicine, Western Sydney University, Sydney, NSW, Australia. Alzheimer's disease (AD) is characterised by beta-amyloid (Aβ) plaques and neurofibrillary tangles as well as neurodegeneration, neuroinflammation, and oxidative damage. AD patients exhibit various behavioural and cognitive symptoms including social withdrawal and memory loss. The phytocannabinoid cannabidiol (CBD) possesses antioxidant, anti-inflammatory and neuroprotective properties and prevents Aβ-induced neuroinflammation, and tau hyperphosphorylation in vitro. CBD also reverses cognitive deficits of pharmacological Aβ models. Thus, CBD may offer therapeutic value for AD. We determined the remedial as well as preventative effects of CBD in a double transgenic mouse model of AD (APPxPS1 transgenic mice). Animals were treated with CBD (20 mg/kg) either a) orally for 8 months before the onset of AD symptoms or b) i.p. for 3 weeks post development of AD symptoms. Control and APPxPS1 transgenic mice were then tested in various cognitive domains and their brains analysed for AD-relevant pathology. CBD a) prevented the development of a range of cognitive deficits typically seen in AD transgenic mice (e.g. spatial and recognition memory deficits) and b) was also able to reverse those impairments once established in transgenic mice. Brain analyses suggest that CBD's impact on neuroinflammation might be involved in this beneficial effect. CBD might have therapeutic potential for AD, which is highly relevant, as it has already been tested in clinical trials. Future research will have to clarify the mechanisms involved further.

19. **Flumazenil effects on c –fos expression in striatum of rats with associative tolerance to midazolam.** Cruz-Morales SE, González-Sánchez DJ, Castillo-Roberto G, Arriaga-Ramírez JPC. UNAM, FES-Iztacala, Psicofarmacología. Benzodiazepines (BZ) are used in the treatment of anxiety, its repeated use produces tolerance. Tolerance can be pharmacological (when drug is administrated and evaluated in the same context the effects are reduced) or associative (when drug is administrated and evaluated in different context tolerance drug is not seen). Tolerance to benzodiazepines is context dependent, so it is important to study the changes related with different types of tolerance. Immunohistochemical technique detects the presence of Fos protein when neurons are activated.

Therefore, the objective of this study was to evaluate the expression of c-Fos in the striatum in the development of associative and no associative tolerance in subjects exposed to the elevated plus-maze (EPM) after chronic treatment with midazolam (M), and the administration of flumazenil antagonist in two different contexts. The subjects (Ss) were Wistar male rats assigned to 7 groups: a group with saline (S), two groups evaluated in different contexts, Colony room (C) or Laboratory (L), one from each group with acute administration of M (aMC and aML), two groups with chronic administration (20 days) of M (cMC and cML) and two groups with chronic administration of M and co-administration of flumazenil (F) the day of the test, both drugs dose were 1 mg /kg, ip. Ss were exposed to the EPM for 5 min and then sacrificed, 2hr later were perfused, the brains were dried and subjected to immunohistochemistry. The anxiolytic effect of M was detected; both the development of tolerance and the effects of flumazenil were context dependent. The C-Fos expression was lower in the groups with acute administration of M; in chronic groups and in the group with flumazenil c-Fos expression increased and also was context-dependent. The data suggest the involvement striatal expression of associative tolerance BZ. UNAM, DGAPA, PAPIIT IN307711.

20. **Effects of GABA-B Receptor Modulation in a Model of Chronic Inflammation.** Murtishaw, Andrew S.1; Bolton, Monica M.1; Heaney, Chelcie F.1, Langhardt, Michael A.1; Belmonte, Krystal Courtney D.1; Boren, Austin J.1; Calvin, Kirsten N.1; Kinney, Jefferson W.1. 1 University of Nevada, Las Vegas. Prolonged neuroinflammation has been associated with a number of neurodegenerative diseases, including Alzheimer's disease (AD). Excessive activation of glial cells, namely microglia and astrocytes, has shown to be a consistent pathological hallmark in the brains of AD patients. Recently, studies have shown that astrocytes are able to synthesize and release the inhibitory neurotransmitter GABA and microglia cells, the primary immune cells of the brain, have been shown to express GABA-B receptors. Early characterizations of AD first described alterations in astrocyte location and activation in the disease as well as more recent reports that indicate differences in the total abundance of GABA within the brains of AD patients. Combined, these data provide support for the hypothesis that astrocytes regulate microglia activity through the release of GABA acting at GABA-B type receptors. The activation of GABA-B on microglia may serve to reduce the activation status of these microglia, thereby reducing the number of pro-inflammatory cytokines present within the brain. In the present study, we examined the effects of the GABA-B agonist baclofen on chronic inflammation in rodents administered lipopolysaccharide (LPS). LPS is a bacterial endotoxin derived from the cell wall of gram-negative bacteria and is capable of mounting an immune response through the activation of toll-like receptor 4 (TLR4). Our data indicate that the administration of baclofen initially attenuated the pyrogenic effects of LPS administration, though this effect was lost after two weeks of injections. The administration of baclofen also rescued deficits in spatial learning and memory seen in animals chronically administered LPS. Various inflammatory markers were evaluated, including cytokines and activated microglia. These preliminary data provide support that the modulation of GABA-B receptor function may alter the immune response evoked by activation of TLR4. These data may also provide support for a potential role of GABA-B in modulating aberrant immune activity seen in AD populations.

21. **Role for hypothalamic projections to habenula in obesity.** Richard M. O'Connor and Paul J. Kenny. Department of Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, New York, NY, U.S.A. Rates of obesity are on the rise worldwide, resulting in a growing threat to public health1. Pharmacotherapies that safely reduce body weight in obesity remain elusive, partially due to our incomplete knowledge of neural mechanisms that control the feeding behaviors that drive obesity. The lateral hypothalamus (LH) plays a critical role in energy homeostasis. Indeed, electrical stimulation of LH induces feeding in satiated rodents while LH lesions result in voluntary starvation2. The LH plays a key role in regulating sensitivity to reward. We found that the development of obesity in rats is associated with the emergence of a profound brain reward deficit, measured by elevated LH self-stimulation thresholds in rats3. In addition, obese rats demonstrate markedly reduced willingness to work for food rewards. Precisely how LH influences brain reward function and the value of food, and by extension its role in obesity, remains unclear. The habenula is a distinct set of nuclei linking forebrain and midbrain structures

and is divided into two principal parts termed the medial habenula (MHb) lateral habenula (LHb). The LHb has been described as a “preference center” which exerts a negative influence over motivated behaviors through inhibition of midbrain dopamine neurons. A major input to the LHb originates in the LH, providing a potential mechanism by which the LH can influence brain reward function and the motivational value of food. Here, we tested the hypothesis that LH projections to LHb play an important role in food preference and the development of food-relevant motivational deficits in obese rats. To target the LHb-LH pathway, we delivered an AAV2/5-Cre-eYFP virus into the LHb, this travels in a retrograde fashion to express Cre recombinase in the cell bodies of LHb projecting neurons. A Cre-inducible diphtheria toxin (DTA) was then delivered to the LH, selectively ablating LH neurons that project to LHb. In a separate set of experiments we delivered Cre-inducible “excitatory” (hM3Dq) Designer Receptors Exclusively Activated by Designer Drugs (DREADD) to LH instead of Cre-inducible DTA. This allowed for stimulation of the LH-LHb circuit via administration of clozapine-N-oxide (CNO) which exclusively stimulates DREADDs. We found lesioning of the LH-LHb pathway in rats decreased the motivational value of food in a manner similar to that observed in obese rats, reflected by a decreased willingness to work for food rewards and decreased home cage chow consumption. Conversely stimulating the LH-LHb circuit increased the willingness of rats to work for food rewards and increased home-cage chow consumption. These findings identify the LH-LHb pathway as an important brain circuit involved in regulating feeding. Currently, we are seeking to identify LHb neurons that transduce food-relevant information and explore adaptive responses in this pathway that may occur during the development of obesity. 1 Finkelstein, E. A., Ruhm, C. J. & Kosa, K. M. Economic causes and consequences of obesity. Annual review of public health 26, 239-257, doi:10.1146/annurev.publhealth.26.021304.144628 (2005). 2 Olds, J. & Milner, P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. Journal of comparative and physiological psychology 47, 419-427 (1954). 3 Johnson, P. M. & Kenny, P. J. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nature neuroscience 13, 635-641, doi:10.1038/nn.2519 (2010).

22. **Single neuron firing in the rat Amygdala and Piriform Cortex during Social Interaction.** **Francesca Pibiri1, Steven Poulter1, Colin Lever1.** 1Psychology Department, University of Durham. The increasing prevalence of Autistic Spectrum Disorders (ASD) and the need for rodent as well as primate models of ASD strongly suggest the importance of understanding the neuronal bases of rodent social interaction. We use single-unit recording to investigate neuronal firing patterns in two inter-connected regions: the amygdala and the anterior piriform cortex. Dysfunction in the amygdala has been explicitly implicated in ASD. Olfactory signals strongly shape rodents’ social interaction: previous anatomical and physiological studies implicate the piriform cortex in olfactory pattern separation and pattern completion functions which could support memory for the odour profile of familiar conspecifics. As a first step in characterising the rodent social amygdala and piriform cortex, we pair Lister Hooded rats in an apparatus where they are fully free to engage in a variety of positive social interactions (including anogenital sniffing, face to face contacts, following, walking over, allogrooming), with typically infrequent aggressive behaviours. The apparatus is a 40x40 cm wooden square box with a wall height of 50 cm. We perform extracellular electrophysiological recordings from ensembles of single neurons tested in various social and non-social conditions (e.g. familiar rat in box vs empty box, or familiar rat vs novel rats). In addition, we simultaneously record behaviour with images time-stamped in synchronization with the electrophysiological recordings. Preliminary results show that there are pyramidal neurons in the rodent amygdala and piriform cortex which respond strongly to social interaction. To date we have conducted preliminary analysis from 250 neurons in the piriform cortex and 70 neurons in the amygdala (pyramidal cells or interneurons which fired ≥100 spikes in one or more trials). More than 20% of the cells in the piriform cortex and about 50% of the cells in the amygdala showed changes in the firing rate when a familiar social stimulus was present. Furthermore, the data from one rat revealed that about 20% of the cells in the piriform cortex increased their firing rate when exposed to a novel compared to a familiar rat.

23. **Lanthionine synthetase C-like 2 protein (LANCL2) in the spinal cord is crucial to maintain normal nociceptive behaviors in rats.** Han-Rong Weng and Dylan W. Maixner. Department of Pharmaceutical

and Biomedical Sciences, University of Georgia College of Pharmacy, Athens, GA, USA (Spon: Han-Rong Weng). Maintaining a normal nociceptive behavior is fundamental for animal survival. Nociceptive behaviors are controlled by signaling pathways that transmit nociceptive signals. The spinal dorsal horn is an important center for processing signals related to nociceptive behaviors. In this study, the role of spinal LANCL2 in the regulation of nociceptive behaviors was investigated. We found that LANCL2 was expressed in the spinal dorsal horn. Using immunohistochemistry techniques, we found that LANCL2 was co-localized with the neuronal marker (NeuN), but not the microglial marker (Iba1) or astrocyte marker (GFAP), indicating that the LANCL2 is expressed only in neurons but not in microglia or astrocytes. Rats with genetic knockdown of LANCL2 by siRNA in the spinal dorsal horn exhibited abnormal nociceptive behaviors characterized by hypersensitivity to mechanical and thermal stimuli. To determine whether the behavioral changes induced by the LANCL2 siRNA are associated with neuroinflammation in the spinal cord, Western blotting was used to determine the protein expressions of Iba1, GFAP, ERK, and TNF alpha. In comparison with rats receiving the control siRNA, we found that the protein expressions of Iba1, GFAP, ERK, and TNF alpha were significantly increased, indicating activation of microglia and astrocytes, and increased production of pro-inflammatory cytokines. These findings suggest that LANCL2 plays a crucial role in maintaining normal nociceptive behaviors in rats, and suppression of LANCL2 expression in the spinal cord leads to abnormal nociceptive behaviors via induction of neuroinflammation in the spinal dorsal horn. Acknowledgements: This work was funded by the U.S. National Institutes of Health grant NS 064289 (HRW).

24. **Critical developmental period for the effects of methamphetamine on social behavior of adult male and female rats.** Hrebickova, Ivana; Sevcikova, Maria; Macuchova, Eva; Šlamberová, Romana. Charles University in Prague, Third Faculty of Medicine, Department of Normal, Pathological and Clinical Physiology, Prague, Czech Republic. Social behavior involves complex of different forms interactions between individuals that is essential for healthy mental and physical development throughout lifespan. Psychostimulants, including methamphetamine (MA), have neurotoxic effect, especially, if they are targeting CNS during its critical periods of development. The present study was aimed on evaluation of changes in social interactions following scheduled prenatal and neonatal MA treatment in combination with acute application in adulthood. Eight groups of male and eight groups of female rats were tested in adulthood: rats whose mothers were exposed to MA (5 mg/kg) or saline (SA, 1 ml/kg) during the first half of gestation period (GD 1-11), the second half of gestation period (GD 12-22) and neonatal period (PD 1-11). In order to do so, we compared indirect neonatal application via the breast milk with the group of rat pups that received MA or SA directly by injection. In adulthood, half of animals from each group were injected with MA (1 mg/kg), second half with saline 45 min prior to the Social Interaction Test. Females and males were observed for social and nonsocial activities between two unfamiliar individuals of the same sex and same treatment in a familiar Open field (OF) arena. This study demonstrates that acute dose of MA leads to decrease in social interactions (SI) and increases nonsocial activities in all tested animals. Moreover, our results show sexual dimorphism in response to the drug. Females were significantly more active in OF than males after acute dose of MA. Animals exposed to the prenatal treatment within the second half of gestation (ED 12-22) and throughout early lactation period (PD 1-11) had significantly fewer SI and had higher locomotion and exploratory behavior than animals exposed within first half of gestation (ED 1-11). Thus, our results indicate that adult MA challenge affects social behavior of adult rats in sex-, treatment- and time-of-exposure-specific manner. Supported by: GAUK 88315, SVV/2015, GACR 14-03708S, PRVOUK P34.

25. **Hyper-locomotor activity in the mice lacking in an enzyme synthesizing chondroitin sulfate.** Michihiro Igarashi1,2, Nozumu Yoshioka1,3 Kosei Takeuchi1,4, Keizo Takao5,7, and Miyakawa6. 1Dept Neurochem & Mol Cell Biol, 2Trans-disciplinary Res Program, Niigata Univ Grad Sch Med Dent Sci, Niigata; Japan; 3Fukushima Med Sch, Fukushima; Japan; 4Aichi Med Univ, Nagakute, Aichi, Japan; 5Nat Inst Physiol Sci, Okazaki, Japan; and 6Fujita Med Hlth Univ, Toyoake; Japan; 7Toyama Univ Sch Med, Toyama; Japan. Chondroitin sulfate (CS), a glycosaminoglycan, is a major extracellular molecule in the brain and highly concentrated in the perineuronal nets (PNN), which regulate the synaptic activity and the

plasticity. CS is attached with several core proteins and composed of proteoglycans (CSPG), such as aggrecan, neurocan, versican, and so on. We recently produced the knockout mice lacking in a key enzyme for CS synthesis, CSGALNACT1. Although the mice have slightly shorter body lengths by the abnormal development of skeletons, they are viable and fertile. We analyzed the mice morphologically and biochemically, and revealed that PNN was impaired and CS accumulation there was much reduced in various regions of the brain. The amount of CS was decreased by maximally 50%. Histochemical studies revealed that CS in PNNs were also reduced in these mice. We performed the behavioral analysis using the test battery and found that the mice had a hyper-locomotive activity. Taken together, our results suggest that CS synthesis is related to higher brain functions such as the locomotive activity.

26. **Social play behavior in juvenile rats after neonatal exposure to methamphetamine.** Mária Ševčíková, Anna Holubová, Ivana Hrebíčková, Romana Šlamberová. Charles University in Prague, Third Faculty of Medicine, Department of Normal, Pathological and Clinical Physiology, Prague, Czech Republic. Methamphetamine (MA) belongs to the most abused drugs. The popularity of this drug among women, and pregnant women as well, seems to be due its psychostimulant and anorectic effects. Suckling neonates can also be exposed to MA postnatally since MA is secreted in the mother´s breast milk. The neonatal period in rats corresponds in the development of the nervous system to the third trimester in humans. The aim of our study is to determine the effect of MA exposed during 11 days after birth to the social play. Social play is an integral part of the development of social behavior, marker of creating the hierarchy and cohesion of the group. Additionally, social play is known to be modulated by neurotransmitters system involved in reward and motivation. Pups receiver MA during postnatal days (PD) 1-11 either directly (in dose of 5mg/kg s.c.) or indirectly via the breast milk of the mother (the same dosage). The control groups received saline in the same way. On the PD 28 and 29, the pups were individually habituated to the test cage for 10 min. Subsequently, the animals were socially isolated during the night before the testing day. On the PD 30, the pups were treated with MA (acute dose of 1mg/kg s.c.) or saline 45 minutes before testing. The test consisted of placing 2 similarly treated animals of the same sex into the test cage for 15 min. The frequency and duration of social play behavior, which consists of pinning and pouncing, was influenced by the interaction between the neonatal drug treatment and the type of its administration. Males who received neonatal MA directly pounced less frequently compared to direct application of saline. Males who received neonatal saline indirectly played more frequently and longer than females of the same treatment. The acute application of MA eliminated social play in all the groups. There were no differences in the duration of social exploration without play behavior. Thus it seems that the social play behavior is influenced by the interaction between neonatal treatment and the type of application and the acute dose of MA suppresses the social play. Supported by: GAUK 88315, GAČR 14-03708S and PRVOUK P34.

27. **Changes in gut microbiome during development of behavioral sensitization to the dopamine agonist quinpirole.** Szechtman, Henry; Jung, Tony; Jung, Paul; Raveendran, Lucshman; Farbod, Yasamin; Sakic, Boris; Dvorkin-Gheva, Anna; Surette, Michael. McMaster University, Hamilton, ON, CANADA. Rather than tolerance, repeated exposure to dopamine stimulants may lead to an enhanced motor response, a phenomenon known as behavioral sensitization. For example, chronic treatment of rats with the dopamine D2/D3 agonist quinpirole increases the locomotor response to this drug to levels that are several times higher than after acute treatment. It has been suggested that quinpirole-induced sensitization reflects, in part, an augmented effect of the drug on a central dopaminergic system controlling energy expenditure, a notion consistent with empirical findings that in quinpirole sensitized rats energy metabolism is shifted away from carbohydrates in favor of fat utilization, as measured by VCO2/VO2 respiratory quotient. Here we report findings suggesting a plausible peripheral mechanism contributing to the shift in energy metabolism induced by chronic treatment with quinpirole, and in particular, a drug-induced modification in the composition of gut microbial populations. Methods: Two groups of rats received 9 injections of saline (n=16) or quinpirole (n=15; 0.25 mg/kg), at weekly intervals for the first 5 weeks and then 2 injections per week until end of treatment. After each injection, rats were placed on a large open field for 55 min and their behavior was video recorded for subsequent analysis.

Fecal matter was collected after each trial and frozen for bacterial community profiling of the 16S rRNA gene using paired end reads of the V3 region. Results: As expected, quinpirole induced locomotor sensitization. During the course of the experiment, a number of significant shifts in gut bacterial composition were observed in both groups, as well as differential changes due to quinpirole. Of note, quinpirole raised the relative abundance of Lachnospiraceae (g). Members of this family have been implicated in energy metabolism. Conclusion: Peripheral sites of action by dopaminergic stimulants may contribute to the observed behavioral effects of psychostimulant drugs by altering gut microbiota. Supported by the Ontario Mental Health Foundation (OMHF).

28. **Signaling by tuberoinfundibular peptide of 39 residues in the medial amygdala modulates male aggressive behaviors.** Mumeko C. Tsuda, Ted B. Usdin. Section on Fundamental Neuroscience, NIMH, NIH, Bethesda, MD. Impaired social interactions have a tremendous deleterious impact on human society as well as the directly affected individuals. Thus, it is important to understand the neurobiological bases of, and circuits that regulate, social behaviors. Based on recent anatomical evidence, tuberoinfundibular peptide of 39 residues (TIP39) and its receptor, parathyroid hormone 2 receptor (PTH2R), a peptide-receptor neuromodulator system, may play a role in modulating male social behaviors. While examining the phenotype of adult PTH2R knockout male mice (KO), we observed increased social investigation towards a cylinder containing a male stimulus mouse (social investigation test, SIT), decreased aggression towards a stranger male mouse introduced into their home-cage (resident/intruder test) and more submissive behaviors in one-to-one competitions (social dominance tube test) compared to wild-type mice. PTH2Rs synthesized by local neurons and TIP39 containing terminals on projections from a group of distant neurons are abundantly present in the medial amygdala (MeA), a brain region with an established role in regulating male social behaviors. We therefore asked whether TIP39 signaling via PTH2Rs in the MeA modulates the male social behaviors that were changed in the KO male mice. Using the designer receptor exclusively activated by designer drug (DREADD) approach, we stereotaxically injected the MeA of male mice that express Cre-recombinase in PTH2R-expressing neurons with a Cre-dependent Gi-coupled DREADD virus that can inhibit neuronal activity. One hour after systemic administration of saline or clozapine-N-oxide (CNO), a selective DREADD agonist, we evaluated either (1) social investigation towards a cylinder containing a male or female mouse in the SIT, (2) intermale aggression in the resident/intruder test, or (2) dominant/submissive behaviors in the social dominance tube test. First, we found that inhibiting PTH2R neurons in the MeA with CNO at the time of SIT increased social investigation duration towards another male mouse, but not female mouse compared to saline treated control mice. However, inhibiting PTH2R-expressing neurons in the MeA with CNO reduced levels of intermale aggression and increased submissive behaviors in one-to-one competitions compared to saline treated mice. Collectively, findings from this study are the first to demonstrate that TIP39 signaling via PTH2Rs in the MeA contributes to the regulation of male aggressive behaviors.

29. **Sex-dependent behavioral effects of isolation-rearing.** F. Scott Hall, Dawn Muskiewicz, Dankesh Joshi, Federico Resendiz Gutierrez, Natasha Hall, Yasir Saber. Dept. Pharmacol. & Exp. Therapeutics, Coll. Pharm. & Pharm. Sci., Univ. of Toledo, OH, USA. Background: Social isolation of mice after weaning (isolation-rearing) has been suggested to produce a variety of pathological behavior phenotypes. In particular, it has been suggested to produce behavioral impairments indicative of a hyperdopaminergic state (hyperlocomotion and increased responses to psychomotor stimulants), and behavior indicative of reduced serotonin function, anxiety and depressive-like behavior. Some data suggests that males and females respond differently to this experience, and may represent sex-dependent differences in the propensity to develop certain psychiatric conditions. Methods: At the age of 21 days of age, male and female C57BL/6J mice (N=10 per experimental condition) were rehoused singly or in groups of 3-4 mice. Subjects remained in these conditions for 8 weeks. At this time they were subjected to several behavioral tests of anxiety (elevated plus maze, open field, and light-dark test) and to testing for prepulse inhibition of the acoustic startle response (PPI). Results: Sex-dependent effects on some measures of anxiety, but not all measures, were observed in these tests. Most notably, isolation-reared female, but not male, mice spent less time in the center of an open field, indicative of increased anxiety in these mice. Isolation-

reared female, but not male, mice also spent significantly more time in the closed arms of the elevated plus maze than socially reared female mice. In the light dark test isolation-reared female, but not male, mice had fewer transitions between the light and dark zones. In contrast to these effects on anxiety, isolation-rearing did not affect PPI in female mice, but did produce reduced PPI (at the lowest pre-pulse intensity) in male mice. Discussion: The present experiments found evidence that the effects of isolation-rearing are sex-dependent. (1) Isolation-reared female, but not male, mice were less active in the center of an open-field, indicative of increased anxiety. (2) Isolation-reared male, but not female mice, had deficits in PPI, an animal model of sensorimotor gating indicative of hyperdopaminergic function. Collectively, these data suggest that early social isolation has distinctly different effects in male and female mice.

30. **Mechanisms underlying the effects of Synthetic Psychoactive Cathinones.** F. Scott Hall1, Omar Issa1, Dawn Muskiewicz1, Yasir Saber1, Natasha Hall1, Joseph Yager1, Taylor Osting1, Ying-Shan Piao2, Ichiro Sora3. 1Dept. Pharmacol. & Exp. Therapeutics, Coll. Pharm. & Pharm. Sci., Univ. of Toledo, OH, USA; 2Dept. Geriatrics, Capital Medical Univ., Beijing, China; 3Dept. Psychiatry, Kobe Univ., Kobe, Japan. Background. Synthetic psychoactive cathinones (SPCs) are drugs with psychostimulant and entactogenic properties similar to other amphetamines. Abuse of SPCs is a substantial public health problem associated with adverse events, emergency room admissions, and lethal overdoses. Whether these drugs present a greater risk than methamphetamine (METH) or 3,4-methylenedioxymethamphetamine (MDMA) is unknown. SPC actions are mediated by transporters for dopamine (DAT), serotonin (SERT), and norepinephrine (NET), where these drugs act as releasers (amphetamine-like) or blockers (cocaine-like). The psychoactive effects of SPCs are similar to MDMA and METH. Hyperthermia is an important factor in the lethal and neurotoxic effect of amphetamine-like drugs, but its importance relevant to other effects is debatable and may differ across compounds. Methods. In an effort to understand the mechanisms underlying the toxic, lethal and hyperthermic effects of SPCs we conducted an initial study in DAT and SERT knockout (KO) mice, examining methylone (2-methyamino-1-[3,4-methylenedioxy-phenyl]propan-1-one). Results. Methylone had an LD50 lower than that previously observed for METH and MDMA, producing a 2 °C increase in temperature, similar to METH. The lethality produced by an LD50 dose of methylone was substantially reduced in DAT KO mice, but unaffected in SERT KO mice. Importantly, methylone-induced hyperthermia was not different in DAT KO mice, while it was slightly greater in SERT KO mice. By contrast, the selective D1 receptor antagonist SCH 23390 and the selective D2 receptor antagonist raclopride reduced methylone-induced hyperthermia, but there appeared to be hypothermic effects in saline treated subjects as well. Conclusions. These data clearly dissociate the lethal and hyperthermic effects of methylone, suggesting that factors other than hyperthermia are critical. Ongoing studies compare the LD50s of a range of other SPCs, also examining their effects on a variety of organs in an attempt to identify which effects that might be mediators of METH, MDMA, and SPC lethality.

31. **Harmonic resonances in EEG from human participants entrained to photic flicker.** Thalheimer, W., Storrs, T., Candelaria, D., Cocchieri. C., Saia, D., Da Silva, B., Flores, M., Flores, J., Danbury, M., and Rossi III, J. Florida Gulf Coast University, Ft. Myers, FL. Last year we reported results from experiments on cortical EEG frequency entrainment to a photic stimulus flickering at varying frequencies in the alpha-band (7.0-12.5Hz). While each of the 15 experimental participants in the study exhibited significant entrainment in the alpha-band in excess of 500% when compared to baseline, the flicker frequency to which the participants entrained differed among the participants. In addition, we found that nine of the 15 participants reliably exhibited entrainment to more than one flicker frequency. During initial power analyses in determination of the entrainment frequencies, we noticed that the power spectra from many participants exhibited peaking at frequencies extending well into the beta band (13-30Hz). Subsequently, we analyzed 180 records (15 subjects x 12 flicker frequencies) composed of 12-bit data recorded from one electrode (157mm2) placed just superior to the external occipital protuberance, digitized at 512Hz. The records were analyzed in 0.5Hz bins centered around frequencies from 7 - 30Hz in 0.5Hz increments using Matlab. For each of the 12 flicker stimulation frequencies (7.0Hz-12.5Hz in 0.5Hz increments)

between 46 and 87% of the records exhibited significant peaking at the flicker frequency. Of these, 76% exhibited peaking at the first harmonic above the stimulation frequency, and 39% exhibited peaks at the second harmonic. Two of 15 records for both 7.0Hz and 7.5Hz exhibited peaks at the third harmonic. Additionally, 14 of the records that failed to exhibit peaks at the stimulation frequency, exhibited a harmonic series starting at some other frequency. These results were surprising in that they clearly weren't produced by electrical or experimental artifacts, indicating a tendency for entrained occipital cortex to be sensitive to harmonic resonance. That harmonic resonance in visual cortex has been previously found in both cats and humans and has been postulated to be important for cognitive processing of visual events (Herrmann, 2001), suggests a strategy for presentation of visual stimuli to individuals with known entrainment frequency profiles in recognition and decision experiments. We are currently evaluating that strategy.

32. **Convulsions induced by methyl ß-carboline-3-carboxylate (ß-CCM) in mice: effects of preceding saline injections.** 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. The convulsive effects of a high (5 mg/kg i.p.) dose of the GABA inverse agonist methyl ß-carboline-3-carboxylate (or ß-CCM), preceded or not by the administration of two lower doses of ß-CCM (0.5 and 1 mg/kg i.p.) or of saline solution were studied in 9 inbred strains of mice. In 5 of the strains (A/J, BALB/c By, C3H/HeJ, CBA/H and DBA/2J), neither saline, nor preceding injections of ß-CCM had any effect on subsequent reactivity to the subsequent convulsive dose. In the other 4 strains, such injections induced either tolerance (CPB-K, NZB), or sensitisation (C57BL/6J, XLII), whatever the compound subsequently administered (ß-CCM or saline). These data rule out, in these strains, any tolerance or sensitisation effect due to ß-CCM, but suggest that such effects could be due to injection per se.

33. **Dissociable roles for basolateral amygdala and orbitofrontal cortex in optimal choice behavior under conditions of reward variability.** Alexandra Stolyarova1, Alicia Izquierdo1. 1 University of California, Los Angeles. All animals make choices based on expected outcome values and adjust their behavior when reward conditions change: upshifts in value facilitate, whereas downshifts suppress responding. The basolateral amygdala (BLA) and orbitofrontal cortex (OFC) both participate in outcome valuation but their specific roles in this process are frequently difficult to dissociate. In the present work we first performed computational analyses of trial-by-trial performance of OFC- and BLA-lesioned rats in pairwise discrimination reversal learning. We found a specific detrimental effect on long-term inferred outcome value resulting from OFC lesions that recapitulated the performance impairment. Conversely, BLA was uniquely responsible for setting the value update rate. This update rate was dynamically adjusted in response to experienced outcome variability in control animals, but not in BLA-lesioned rats. These results suggest that adaptive choice behavior depends on both the mean and variance of outcome distribution. To then systematically test the effect of variability on behavioral adaptations we developed a novel decision making task using touchscreen response in rats, in which outcome values were determined by normally distributed delays to reward receipt. Rats were presented with two options identical in mean (1 sugar pellet/ 10s) but different in the variance of outcome distribution (high variability, HV vs. low variability, LV). Following the establishment of stable performance, rats experienced reward upshifts (1/ 5s with variance kept constant) and downshifts (1/ 20s) on each option independently, followed by a return to baseline conditions. Rats distributed their choices uniformly at baseline and significantly changed their preference in response to all shifts, suggesting that they were able to infer mean option values despite variability in outcomes. Critically, choice adaptations were asymmetrical: HV potentiated responses to upshifts, but dampened the effects of downshifts. To assess the OFC-BLA mechanisms of these responses, in a separate cohort of animals we evaluated reward mean- and variability-induced neuroadaptations by quantifying the region-specific expression of GluN1 and gephyrin (a reliable proxy for membrane-inserted GABAA receptors). Gephyrin was downregulated in OFC in response to experienced reward mean regardless of variability, consistent with proposed role of this brain region in inferring overall outcome values. Conversely, reward-induced GluN1 and gephyrin upregulation

in BLA was variability-dependent, with the highest levels in the HV group, supporting a role for BLA in adaptations to both outcome mean and variability. Taken together, our findings demonstrate dissociable roles for OFC and BLA in dynamic outcome valuation guiding optimal choice behavior. Support: UCLA Division of Life Sciences Recruitment and Retention Fund (Izquierdo).

34. **Behavioral characterization of neuropeptide S-deficient mice in animal paradigms of pathological fear.** Małgorzata H. Kołodziejczyk1, Josephine Germer1, Evelyn Kahl1 & Markus Fendt1,2, 1Institute for Pharmacology and Toxicology & 2Center of Behavioral Brain Sciences, Otto-von-Guericke University Magdeburg, Germany. Dysfunctions within the mechanisms underlying fear can lead to pathological fear, i.e. anxiety disorders. Currently, the gold standard treatment is a combination of cognitive-behavioral therapy and pharmacotherapy. However, the established pharmacological anxiolytic treatments are not very optimal due to limited efficiency and negative side-effects. Moreover, the neurobiological underpinnings of most anxiety disorders are as yet not completely understood. Neuropeptide S (NPS), that has been shown to exert strong anxiolytic effects upon intracerebral injection in rodents, seems to be a promising target for anxiety disorders. Several clinical studies identified a polymorphism in the NPS receptor (NPSR) gene that is associated with an increased incidence of anxiety disorders. In this study, we investigated NPSR-deficient mice in two different animal paradigms of post-traumatic stress disorder (PSTD): (A) Mice were fear-conditioned with a single intense electric stimulus and expression of contextual fear was tested 1 or 4 weeks later (experiment 1). (B) Mice were fear-conditioned (two intense electric stimuli) with or without systemic injections of corticosterone (30 minutes after conditioning) and expression of contextual fear was tested 1-2 days later (experiment 2). In these expression tests, animals were exposed to the original conditioning context but also to a very similar context and a different context in order to assess the specificity of contextual fear memory. During different stages of the experiments, blood samples were collected to determine corticosterone levels. Our data show that mice exhibit a PTSD-like fear memory, i.e. a fear generalization, 4 weeks after fear conditioning (experiment 1) or after fear-conditioning in combination with corticosterone injections (preliminary data; experiment 2). In general, high corticosterone levels seemed to be associated with this PTSD-like fear generalization in the two experiments. NPSR-deficient mice have lower baseline corticosterone levels but seemed to have a more pronounced increase in corticosterone levels after the manipulations leading to more pronounced fear generalization.

35. **Effects of lipopolysaccharide administration on performance deficits in the 5-choice serial reaction time task are augmented in socially-isolated rats.** Wendy K Adams1, Eva Harris1, Fiona D Zeeb1, Matthew D Taves1,2, Kiran K Soma1,2, Catharine A Winstanley1. 1Department of Psychology, Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC, Canada; 2Department of Zoology, University of British Columbia, Vancouver, BC, Canada. Social isolation, an established risk factor for the development of mental illness, is associated with impairments in immune function. Indeed, increasing evidence suggests that neuroinflammatory processes contribute to mood and cognitive symptoms of mental illness, possibly via cytokine-induced modulation of neural activity. Lipopolysaccharide (LPS) is an inflammatory component of gram-negative bacteria that elicits the physiological and behavioural symptoms of infection, providing a useful tool to assess the effects of immune activation on brain function in rodents. Since LPS-induced alterations in circulating cytokines differ between rats under isolated or group housing conditions, we set out to explore the effects of LPS and social home cage environment on cognitive performance in the 5-Choice Serial Reaction Time Task (5CSRTT). Male Long-Evans rats reared in pairs (n=12) or in isolation (n=12) were trained on the 5CSRTT as adults; effects of saline and LPS (150 µg/kg) administration were assessed over two dosing rounds separated by a 2-week washout period. A different cohort of animals (pair, n=12; isolate, n=12) was used to examine LPS-induced changes in cytokines and corticosterone in serum and brain samples. Compared to pair-housed rats, social isolation did not alter rats' ability to learn the 5CSRTT. LPS-induced sickness behaviours, indexed by observation of home cage activity for 2 hrs between injection and testing, were augmented in socially-isolated rats. In the 5CSRTT, this enhanced sickness response translated to increased omissions and slower response times in socially-isolated, but not pair-housed,

rats. In addition, social isolation reduced overall levels of impulsive responding, and this was also diminished by LPS administration in both housing groups. In contrast, discriminative accuracy, latencies to collect rewards, and total trials were unchanged by housing condition or LPS administration, and LPS increased perseverative responding in pair-housed rats only. With the exception of reduced impulsivity in isolation-housed rats, these behavioural effects were not apparent in the second dosing round, highlighting the tolerance-like effects of repeated LPS injections on behaviour. In a behaviourally-naïve cohort, social isolation potentiated the induction of corticosterone release by LPS administration and the profile of circulating cytokines also differed between groups; these peripheral data will be compared to that obtained from brain tissue samples in efforts to understand the neural basis of behavioural effects. Collectively, these findings are consistent with the adaptive response of reduced motivational drive under states of immune challenge, and demonstrate that social isolation is an exacerbating factor for such physiological and behavioural changes. Funding source: Canadian Institutes for Health Research.

36. **Effect of beta-asarone on impairment of spatial working memory and apoptosis in the hippocampus of rats exposed to chronic corticosterone administration.** BOMBI LEE1, INSOP SHIM1,2, HYEJUNG LEE1 AND DAE-HYUN HAHM1,2, 1Acupuncture and Meridian Science Research Center, College of Korean Medicine, Kyung Hee University, Seoul, 130-701, Republic of Korea. 2The Graduate School of Basic Science of Korean Medicine, College of Korean Medicine, Kyung Hee University, Seoul, 130-701, Republic of Korea. β-asarone (BAS) is an active component of Acori graminei rhizoma, a traditional medicine used clinically in treating dementia and chronic stress in Korea. However, the cognitive effects of BAS and its mechanism of action have remained elusive. The purpose of this study was to examine whether BAS improved spatial cognitive impairment induced in rats following chronic corticosterone (CORT) administration. CORT administration (40 mg/kg, i.p., 21 days) resulted in cognitive impairment in the avoidance conditioning test (AAT) and the Morris water maze (MWM) test that was reversed by BAS (200 mg/kg, i.p). Additionally, as assessed by immunohistochemistry and RT-PCR analysis, the administration of BAS significantly alleviated memory-associated decreases in the expression levels of brain-derived neurotrophic factor (BDNF) and cAMP-response element-binding protein (CREB) proteins and mRNAs in the hippocampus. Also, BAS administration significantly restored the expression of Bax and Bcl-2 mRNAs in the hippocampus. Thus, BAS may be an effective therapeutic for learning and memory disturbances, and its neuroprotective effect was mediated, in part, by normalizing the CORT response, resulting in regulation of BDNF and CREB functions and anti-apoptosis in rats.

37. **En route to delineating the hippocampal contributions to spatial learning.** Steven Poulter1, Joe Austen1, Yutaka Kosaki2, Colin Lever1, Anthony McGregor1. 1University of Durham, U.K., 2Keio University, Japan. What learning processes are (not) supported by the hippocampus? We sought to address this by determining the pattern of improvements, as well as deficits, that hippocampal lesions induce in the watermaze. In Experiment 1, a hidden goal location was defined by various stable cues including two landmarks suspended above the pool, one directly above the goal. Hippocampal-lesioned rats were deficient in acquiring this goal location. Subsequently, we occluded room cues, rotated the landmarks, and tested for preferential swimming below the now-shifted, goal-defining landmark. Theories positing hippocampal roles in 'flexible' learning would predict hippocampal-lesion induced deficits in this task. Actually, while shams performed moderately, hippocampal-lesioned rats performed even better. Overall, Experiment 1 supported a theory emphasising a hippocampal role in spatial, but not landmark, learning. What sensory inputs support such spatial learning? Influential theories suggest the hippocampus particularly drives navigational strategies based on self-generated motion (SGM). Such theories successfully predict hippocampal-lesion induced deficits in path integration and spatial processing of information 'en route' to a goal (e.g. 'getting there'). Conversely, though, if the hippocampus drives SGM-based navigational strategies, but SGM-cue reliability is disrupted, then the intact hippocampus could cause spatial learning deficits, by outputting an intact stream of 'en route' information that is actually unhelpful. Accordingly, we disrupted SGM-cue reliability by passively transporting rats to a goal, and tested two counter-intuitive predictions: first, that hippocampal lesions should improve passive-

placement based spatial learning (Experiment 2); second, that placing rats inside a box all the way to the goal, and thus disengaging 'en route' processing, should improve this spatial learning in hippocampal-intact rats (Experiment 3). Both predictions were confirmed. Finally, further tests following Experiments 1 and 2 showed strong hippocampal-lesion deficits in spatial learning based on environmental geometry. In summary, our novel pattern of findings is best explained by theories emphasising the hippocampal role in spatial learning sensitive to information from SGM and environmental boundaries, but not landmarks.

38. **Relief learning requires a coincident activation of dopamine D1 and NMDA receptors within the nucleus accumbens.** Jorge R. Bergado Acosta1, Evelyn Kahl1, Georgios Kogias1,2, Taygun Uzunezer1,2 & Markus Fendt1,3. 1Institute for Pharmacology and Toxicology, 2Integrative Neuroscience Program, 3Center of Behavioral Brain Sciences, Otto-von-Guericke University Magdeburg, Magdeburg, Germany. Relief learning is the association of a stimulus with the offset of an aversive event. Later, the then conditioned relief stimulus is able to induce appetitive-like behavioral changes. We previously demonstrated that NMDA receptors within the nucleus accumbens (NAC) are involved in relief learning. The NAC is also important for reward learning and it has been shown that this learning is mediated by an interaction of accumbal dopamine and NMDA receptors. Since conditioned relief has reward-like properties, we hypothesized that acquisition of conditioned relief may also be mediated by a concurrent dopamine D1 and NMDA receptor activation. The present study tested this hypothesis. Therefore, rats received intra-NAC injections of the dopamine D1 receptor antagonist SCH-23390 and the NMDA antagonist AP-5, either separately or together, at different time points of a relief conditioning procedure. First, we showed that SCH-23390 dose-dependently block acquisition but not expression of conditioned relief. In the second experiment, we injected low doses of SCH-23390 and AP-5 either separately or together into the NAC. Co-injections of SCH-23390 and AP-5 blocked acquisition of relief learning, whereas when injected separately, these low doses had no effects. Notably, the co-injections neither affects consolidation nor expression of conditioned relief. Furthermore, they also did not change the locomotor response to the aversive stimuli suggesting that their perception is not changed. This data indicates that a co-activation of dopamine D1 and NMDA receptors in the NAC is required for acquisition of relief learning. This D1/NMDA receptor interaction is known to promote synaptic plasticity. Future studies will investigate which intracellular signaling are involved in the synaptic plasticity underlying relief learning.

39. **Aha-like experience in the rat.** Kenichi Makino1, Yuji Ikegaya1. 1Graduate School of Pharmaceutical Sciences, The University of Tokyo. In the process of solving problems, we gradually learn to cope with problems through trial and error; however there is another form of the learning process, a sudden and striking realization, such eureka, epiphany, and Aha moment. The sudden learning has been studied in primates including humans. In this study, we propose that similar "Aha-like" epiphany is likely to occur in the rat. We used a nose-poke behavior test. One of two nose holes in the front panel in the apparatus is illuminated by green light. When rats poke their noses into the other hole, they are rewarded with a food pellet. In long repetitions of this task, 30% rats showed a sudden increase in the correct rate, while others did not. This ratio is sensitive to the conditions of pre-training, suggesting that the "prepared mind" is important to lead Aha-like epiphany. We video-monitored the behavior of rats during the test. Immediately before the time of the epiphany, the rats exhibited an embarrassed pause before nose poking. These behaviors seem consistent with Aha experience. This study will provide a foothold in elucidating the mechanism of insights.

40. **Learning and memory in the traveling salesman problem in rats.** Marta Stojanovic1, Rachel Blaser1. 1University of San Diego. The traveling salesman problem (TSP) is a combinatorial optimization problem that is used to study spatial cognition in human and non-human animals. Although rats appear to use a distance-minimization strategy in this task, the mechanism by which they solve the task is not yet understood. While the TSP is similar to the radial arm maze and the Morris water maze, it may require different strategies than other popular spatial tasks. Most previous research with the TSP has focused on planning and route selection, but our goal was to determine whether the task could also be useful to study

learning and memory. Rats were given five days of training with each of three different TSP arrays, and then given a memory test at 24, 72, or 120 hours post training. Performance improved significantly across days of training, providing evidence of learning. There was no significant effect of the delay of memory test on the performance of rats. Further research is needed to understand the cognitive processes mediating these effects.

41. **Effects of Acute Ethanol Withdrawal and Intoxication on the Extinction and Reconditioning of Contextual Fear Memories.** Amy R. Williams1 and K. Matthew Lattal1. 1Oregon Health & Science University, OR, USA. Memory can be affected by a variety of illicit substances, including alcohol. Research has shown that acute and chronic ethanol use can either enhance or perturb memory processes. The alteration of memory by ethanol is particularly relevant to Post-traumatic stress disorder (PTSD), as alcohol use disorder is highly comorbid with PTSD. Previously research from our laboratory has shown that acute ethanol withdrawal (AEW, 6 hr following a single 4 g/kg i.p. injection of 20% v/v ethanol) caused impairments in both strong and weak conditioning of contextual fear. The effect of AEW upon memory phases following conditioning remains unknown. Therefore, the focus of this research was to assess how AEW affects extinction and reconditioning in a C57BL/6J mouse contextual fear conditioning procedure. AEW did not significantly affect the formation of an extinction memory, but did cause a loss of rapid reacquisition due to reconditioning that has been demonstrated by ethanol naïve animals. This suggests a disparate effect of ethanol withdrawal on the formation excitatory (conditioning and reconditioning) and inhibitory (extinction) fear memories. Conversely, acute ethanol intoxication (5 min following a single 1.5 g/kg i.p. injection of 20% v/v ethanol) caused a general impairment of reconditioning and in particular conditioning. Further study on the interaction of alcohol withdrawal, intoxication, and fear memory and the neural circuitry involved could inform treatment and prevention of the overlap of these two disorders.

42. **Withdrawn**

43. **Role of muscarinic acetylcholine signaling in G protein-coupled estrogen receptor-mediated social learning facilitation in female mice.** Kelsy Ervin, Wansu Qiu, Tino Topic, Elena Choleris. Dept. of Psychology, University of Guelph, Guelph, ON N1G 2W1 Canada. Social learning is a learning strategy by which animals, including humans, can acquire new information through interaction with or observation of others, without incurring the potential costs of individual, trial-and-error learning. One example of this is social transmission of food preferences (STFP) in rodents, in which an “observer” prefers a novel food it smelled on the breath of a conspecific “demonstrator” over other novel foods. In mice, estrogens enhance learning on this task on both a long-term/genomic time scale, likely primarily through the estrogen receptor (ER) □ (Clipperton et al,2008,Neuropsychopharmacology,33:2372), and on a rapid/non-genomic time scale, primarily through the G protein-coupled ER (GPER) (Ervin et al, 2015, Psychoneuroendocrinology, 58:51). Learning on the STFP depends on acetycholine (ACh) signaling at muscarinic receptors (Boix-Trelis et al,2007,Neurobiol Learn Mem,87:659; Carballo-Márquez et al,2009,Hippocampus,19:446; Carballo-Márquez et al,2009,Neurobiol Learn Mem,91:98), and the GPER is expressed on cholinergic neurons (Hammond et al,2011,Psychoneuroendocrinology,36:182). We therefore hypothesized that estrogens rapidly improve social learning in the STFP by activating GPER and enhancing muscarinic ACh signaling. Female ovariectomized CD1 mice were given treatments of either 17□-estradiol, the GPER agonist G1, or sesame oil control, combined with either 2mg/kg scopolamine (a subeffective dose determined in pilot studies not to impair social learning) or saline. All treatments were given subcutaneously 15min prior to a brief interaction with a previously fed demonstrator mouse. If estrogens improve social learning by enhancing muscarinic acetylcholine signaling, scopolamine pretreatment will block the rapid enhancing effect of 17□-estradiol and G1. Preliminary results suggest that scopolamine treatment does not block the rapid facilitatory effects of 17□-estradiol, however experiments with G1 are ongoing. Our research of estrogens’ interactions with acetylcholine will give us a clearer picture of the downstream mechanisms of their rapid effects on

cognition, as well as the neurobiological mechanisms of social learning. Funded by a grant from the Natural Sciences and Engineering Research Council of Canada (NSERC).

44. **Long-term early life adverse experience affects recognition memory and accelerates the process of habituation to familiar environment.** Anna Holubová1, Anna Mikulecká2, Marie Pometlová1, Kateryna Nohejlová1, Romana Šlamberová1. 1 Charles University in Prague, Third Faculty of Medicine, Department of Normal, Pathological and Clinical Physiology, Prague, Czech Republic, 2 Academy of Sciences of the Czech Republic, Institute of Physiology, Department of Developmental Epileptology, Prague, Czech Republic. Stressful events are believed to be closely associated with the development of psychological alterations and psychiatric disorders. Stress and exposure to glucocorticoids are related with the increase of HPA axis responsiveness early in the life and have been also associated with impairments in learning and memory. Cognitive functions such as memory and learning in animals can be studied on the basis of exploratory behavior of rat to novel and familiar objects. The aim of this study was to evaluate the effect of postnatal stressors to habituation ability and novel object memory in adulthood. Twenty-four rat mothers and twenty-four of their male progeny were used. The mothers were divided into three groups of 10: unstressed control rats (C); rats stressed by social stressor (S); rats stressed by both, social and physical stressors (SW). Behavior of adult (postnatal day 70-80) male rats was tested in the open field arena for three consecutive days. On testing day (TD) 1 and 2 (OFF/OFF) of the experiment three identical objects were exhibited by the animal. On TD 3 (ON), one of the objects was replaced for another one with different color, size and form. The following behaviors were analyzed: a) locomotion – total time spent by walking; b) sniffing – total time spent by sniffing on the floor, walls, objects or in the air; c) rearing – total time spent standing on hind limbs with both forepaws lifted; d) grooming – total time spent by washing or grooming; e) investigation – total time spent by examining a new switched object. Habituation was evaluated as a comparison of behavior on TD 2 relative to TD 1 of experiment. The investigation activity was observed on TD 3. Our results showed the habituation effect in both stressed-groups (S and SW). Specifically, in social-stressed group (S) there was a significant difference only in case of sniffing, while in group of combined stressors (SW) there was an effect in sniffing, rearing and resting. The measurements exhibited a significant difference in exploration of novel object with most active control group (C) and the least active stressed group (SW). In conclusion, our data demonstrate that postnatal exposure of social and physical stressors accelerates adaptation process to familiar environment of adult male rats and decreases their interest of novel object. Supported by: SVV 2016, PRVOUK P34.

45. **Learning impairments produced by embryonic lead exposure persisted in F3 male and female zebrafish.** Xiaojuan Xu1 and Daniel Weber2. 1Grand Valley State University, 2University of Wisconsin-Milwaukee. The zebrafish has become a useful animal model for studying the effects of environmental contaminants on the neurobehavioral development due to its high numbers of eggs per female, ease of breeding, and short generation times. Our previous study showed that embryonic lead exposure produced learning impairments in adult male and female zebrafish. Using avoidance conditioning as the behavioral paradigm, the present study investigated the persistency of learning impairments in adult males and females of the third generation (F3) of zebrafish exposed to lead as embryos. Adult zebrafish were trained to associate light with shocks in a fish shuttle-box consisting of a water-filled tank separated by a divider into two equal compartments. A trial began with the onset of light on the side of the fish's location and the manually raised divider; 12 seconds later mild repetitive electrical shocks were administered. Fish initially swam through the raised divider after receiving several shocks. After repeated trials, fish learned to swim from the lighted end to the dark end before the administration of shocks to avoid the body shock, which is called avoidance response. Two days later, fish were tested for avoidance responses. In Experiment 1, adult F3 males of zebrafish that were exposed to 0, 0.1, 1, or 10 □M lead as embryos were trained and tested for avoidance responses. The results showed that adult F3 males of zebrafish exposed to no lead as embryos learned avoidance responses during training and showed significantly increased avoidance responses during testing. Adult F3 males of zebrafish exposed to lead as embryos showed no significant increases in avoidance responses from training to testing. In

Experiment 2, adult F3 females of zebrafish that were exposed to an identical exposure regimen as in Experiment 1 were trained and tested for avoidance responses. The results showed that adult F3 females of zebrafish exposed to no lead as embryos learned avoidance responses during training and showed significantly increased avoidance responses during testing, while adult F3 females of zebrafish exposed to lead as embryos showed no significant changes in avoidance responses from training to testing. Thus, developmental lead exposure produced learning impairments persisted for generations in both male and female zebrafish. (Supported by NIEHS grant ES04184 and GVSU grant-in-aid)

46. **Post-weaning social isolation results in ultrasonic communication deficits, cognitive impairments and alterations in microRNA-dependent Ube3a1 function on neuronal plasticity in rodents: Implications for autism.** Dominik Seffer1, Henrike Rippberger1, Jeremy Valluy2, Silvia Bicker2, Ayla Aksoy-Aksel2, Martin Lackinger2, Simon Sumer2, Roberto Fiore2, Tatjana Wüst3, Franziska Metge4, Christoph Dieterich4, Gerhard Schratt2, Rainer K. W. Schwarting1, Markus Wöhr1. 1Behavioral Neuroscience, Experimental and Physiological Psychology, Faculty of Psychology, Philipps-University of Marburg, Marburg, Germany. 2Institute of Physiological Chemistry, Biochemical-Pharmacological Center Marburg, Philipps-University of Marburg, Marburg, Germany. 3Interdisciplinary Center for Neurosciences, SFB488 Junior Group, University of Heidelberg, Heidelberg, Germany. 4Max Planck Institute for Biology of Ageing, Computational RNA Biology Lab, Cologne, Germany. Rats are highly social animals and rough-and-tumble play during adolescence has an important role for social development. Post-weaning social isolation, i.e. separation from conspecifics during this phase, is known to induce behavioral phenotypes and changes in neural development relevant to neuropsychiatric disorders like autism. Ultrasonic vocalizations (USVs) are an important component of the rat's social behavioral repertoire and serve as situation-dependent affective signals with important communicative functions. High-frequency 50-kHz USVs are produced in appetitive situations such as rough-and-tumble play and induce social approach behavior, indicating that they serve as social contact calls. Here, we tested by means of our highly standardized 50-kHz USV radial maze playback paradigm if social isolation impairs approach behavior in response to pro-social USVs. Male rats were housed in one of the following conditions: group housing, short-term isolation (24 hours), or long-term isolation (28 days). While group-housed and short-term isolated rats displayed approach behavior in response to pro-social 50-kHz USVs, post-weaning long-term isolation led to pronounced deficits, with rats rather displaying avoidance behavior. Importantly, such deficits could be reversed by one additional week of peer-rearing and were not observed after post-adolescence long-term isolation, indicating a critical period for social development during adolescence. At the neurobiological level, post-weaning isolation, also resulting in poor novel object recognition as expected, led to an increase in an alternative E3 ubiquitin ligase Ube3a transcript, Ube3a1, in the hippocampus; a key regulator of activity-dependent synapse development and plasticity. The increase in Ube3a1 RNA expression following post-weaning isolation was paralleled by elevated levels of microRNA 134, with Ube3a1 knockdown increasing dendritic complexity in the hippocampus in wild-type controls. Ube3a1 RNA knockdown, however, failed to induce dendritic complexity when the miRNA cluster 379-410, including miR-134, was missing, demonstrating that the Ube3a1 function is microRNA-dependent. Taken together, post-weaning social isolation led to ultrasonic communication deficits, cognitive impairments and alterations in microRNA-dependent Ube3a1 function on neuronal plasticity. The finding that environmental factors affecting social behavior and cognition alter Ube3a has important implications, particularly since loss of UBE3A is the leading cause for the neurodevelopmental disorder Angelman syndrome and UBE3A duplications are among the most frequent copy number variations associated with autism.

47. **Application of activation induced manganese-enhanced magnetic resonance imaging (MEMRI) for mapping of brain structures activated by operant behavior in rats.** Gálosi, R.1, Szalay, Cs.1, Aradi, M.2,3, Pál, J.2, Perlaki, G.2,3, Karádi, Z.1,4 and Lénárd, L.1,4. 1Institute of Physiology, Medical School of University of Pécs, Hungary, 2Neurosurgery Clinic, Medical School of University of Pécs, Hungary, 3Pécs Diagnostic Center Ltd, Pécs, Hungary, 4Molecular Neuroendocrinology and Neurophysiology Research Group, Szentágothai Research Center, University of Pécs, Hungary. The manganese-

enhanced magnetic resonance imaging (MEMRI) utilizes manganese ion accumulation in excitable neurons to detect activated brain areas. The goal of the present experiments was to develop a protocol for the application to extend it for operant condition situation with particular attention to the toxicity of manganese and with the expected advantages for the possible detection of the whole-brain responses to the operant behavior in rodents. MnCl2 was intraperitoneally infused in Wistar rats at a dose of 20 mg/kg or an accumulated dose of 40 mg/kg or 60 mg/kg, respectively. Repeated infusions of 20 mg/kg MnCl2 were separated by 24 h to reach the accumulated doses. Effects of MnCl2 were examined on hepatic, somatosensory and motor functions. Cognitive capabilities of the animals were tested in cued visual discrimination operant task. The MEMRI technique was adapted to a 3T clinical MR scanner. T1 maps were calculated before and after MnCl2 administration followed by cued visual discrimination operant task. Changes in T1 values were compared among brain areas of trained animals participating in the water rewarded operant task and naive control rats. Increased serum total bilirubin, aspartate aminotransferase, alanine aminotransferase concentration and decreased albumin level at the dose of 60 mg/kg MnCl2 indicated hepatotoxic effect, while these parameters were within the normal range after the lower doses. The dose of 20 mg/kg and the 40 mg/kg MnCl2 did not have an effect on the accuracy of operant responding. However, both doses enhanced omissions at the end of the operant session indicating a change in motivation and vigor of operant behavior. At last, the developed MEMRI protocol was able to detect activity in brain areas related to the cued visual discrimination operant behavior. The following brain areas showed extensively activation compared to control animal: the visual, somatosensory, motor and premotor cortices, the insular, cingular, ectorhinal, entorhinal, perirhinal and piriform cortices, hippocampus, amygdala with amygdalo-hippocampal areas, dorsal striatum, nucleus accumbens core, pars compacta of the substantia nigra and retrorubral field. In conclusion, the method was able in rats to detect brain regions which are involved in the control of visual stimulus related and reinforced operant responses. Also, the MEMRI has proved to be a reliable method to map brain activity in correlation with the behavior in rodents.

48. **Temporal dissociation of activity-dependent alterations in prefrontal BDNF expression during decision-making shifts.** Robert D. Cole1, Vinay Parikh1. 1Department of Psychology and Neuroscience Program, Temple University, Philadelphia, PA. Brain-derived neurotrophic factor (BDNF) is essential for regulating learning, memory and motivational processes. Evidence suggests that BDNF infusion into the dorsal striatum regulates cognitive flexibility. However, the role of endogenous BDNF signaling in flexible decision-making remains unknown. Activity-dependent alterations in BDNF expression is a key event in synaptic plasticity and cognition. As frontostriatal circuits involving discrete regions of the prefrontal cortex (PFC) and striatum are critical in maintaining different forms of cognitive flexibility, such as strategy shifting (SS) and reversal learning (RL), we hypothesized that shifting to new strategies would produce neuronal activity-dependent alterations in BDNF expression in these circuits. Mice were trained in an operant task requiring the animals to either shift a visual cue-based strategy to an egocentric spatial response-based strategy or to flexibly adapt to a reversal of initial response contingencies. Brains were removed either during the initial learning or after complete acquisition of the new strategy. Quantitative immunohistochemical examined BDNF and cfos expression in the regions of interest. BDNF expression in striatal synaptosomes was examined using immunoblotting. BDNF-positive cell counts increased in the orbito-PFC (oPFC) and medial-PFC (mPFC) following strategy and reversal shifts ($p<.01$). A significant time x behavioral shift interaction was observed ($p<0.01$). During the early phase, an overall increase in BDNF positive cells was noted in all regions irrespective of the shift type. Synaptic BDNF levels also increased in the striatum ($p<.05$) indicating overflow of PFC BDNF to target striatal regions. However, BDNF effects were dissociated based on the shift type following task acquisition. RL was mostly associated with higher BDNF in the oPFC while mPFC prefrontal regions exhibited elevated BDNF expression during SS. Moreover, performance-related increases in BDNF/c-fos co-labeling in the oPFC and mPFC regions were revealed ($p<.01$). Flexible decision-making produces temporal alterations in the frontostriatal BDNF expression. Moreover, the dissociation between cortical region-specific neuronal activity and BDNF levels based on higher-order and lower-order behavioral shift becomes apparent only after the strategy for optimal performance is acquired. As BDNF regulates

synaptic transmission, prefrontal BDNF alterations may play a critical role in modulating corticostriatal activity to maintain shifts in strategies with changing environmental demands. Deficits in frontoexecutive processes like cognitive flexibility are associated with major neuropsychiatric disorders such as schizophrenia, addiction and depression. Therefore, BDNF may serve as a neurobiological substrate for a neurocognitive endophenotype common to multiple psychiatric conditions.

49. **Exogenous ketone supplements reduce anxiety-related behavior in Sprague-Dawley and Wistar Albino Glaxo/Rijswijk rats.** Ari, Csilla 1; Kovacs, Zsolt 2; Juhasz, Gabor 3; Murdun, Cem 1; Goldhagen, Craig R. 1; Koutnik, Andrew 1; Poff, Angela M. 1; Kesl, Shannon L. 1; D'Agostino, Dominic P. 1. 1Department of Molecular Pharmacology and Physiology, Hyperbaric Biomedical Research Laboratory, Morsani College of Medicine, University of South Florida, Tampa FL, USA; 2Department of Zoology, University of West Hungary, Savaria Campus, Szombathely, Hungary; 3Proteomics Laboratory, Eotvos Lorand University, Budapest, Hungary. Nutritional ketosis has been proven effective for seizure disorders and other neurological disorders. The focus of this study was to determine the effects of ketone supplementation on anxiety-related behavior in Sprague-Dawley (SPD) rats. We tested exogenous ketone supplements fed chronically for 83 days and administered sub-chronically for 7 days by gavage, followed by assessment of anxiety measures on elevated plus maze (EPM) on 97 male SPD rats. The groups included standard diet (SD), ketogenic diet (KD) or SD + ketone supplementation. Low-dose ketone ester (LKE) (1,3-butanediol-acetoacetate diester, ~10 g/kg/day, SD+LKE), high dose ketone ester (HKE) (~25 g/kg/day, SD+HKE), beta-hydroxybutyrate-mineral salt (βHB-S) (~25 g/kg/day, SD+KS), and BHB-S + medium chain triglyceride (MCT) (~25 g/kg/day, SD+KSMCT) were used as ketone supplementation. To extend our results on SPD rats, exogenous ketone supplements were also tested on Wistar Albino Glaxo/Rijswijk (WAG/Rij) rats for 7 days by gavage (SD+KE and SD+KS). Behavioral data collection was conducted manually by a blinded observer and with a video-tracking system (SMART V3.0 PLATFORM, Harvard Apparatus) at the end of treatments. Ketone supplementation reduced anxiety on EPM as measured by less entries to closed arms (sub-chronic SD+KS: SPD and WAG/Rij rats), more time spent in open arms (sub-chronic SD+KS: SPD and WAG/Rij rats; chronic SD+KS/KSMCT: SPD rats), more distance travelled in open arms (chronic SD+KS/KSMCT: SPD rats), and by delayed latency to entrance to closed arms (chronic SD+HKE/KS/KSMCT: SPD rats), when compared to control. The chronic and sub-chronic ketone supplements also caused significant elevation of blood βHB levels and changed blood glucose levels. This preliminary data indicates that chronic and sub-chronic ketone supplementation not only elevated blood ketone levels in both animal models, but reduced anxiety-related behavior. These influences may be highly beneficial for patients managing diseases with nutritional ketosis. This work was supported by ONR Grant N000141310062 (DPD), the Natl. Devel. Agency of Hungary TIOP-1.3.1.-07/2-2F-2009-2008 (ZK), the Natl. Devel. Agency of Hungary TÁMOP 4.2.1./B-09/1/KMR-2010-0003, KTIA_NAP_13-2014-0023 (GJ). We thank Tamás Török for technical assistance.

50. **Long-term sexually-dichotomic impact of adolescent CRF hyper-signaling on adult anxiety-like traits and trauma susceptibility.** Toth M1,2,3, Desiree Hoppener4, Geyer MA1,3, Mansuy IM5, Merlo-Pich E6, Risbrough VB1,3. 1University of California San Diego, 2Institute of Experimental Medicine, Budapest, 3Center of Excellence for Stress and Mental Health, Veterans Affairs Hospital La Jolla, 4University of Utrecht, 5Brain Research Institute, University and ETH Zürich, 6Neuroscience Disease Therapeutic Area, Pharmaceutical Division, F. Hoffman – La Roche. There is significant evidence showing the developmental origin of anxiety disorders, as well as their peak during adolescence. It is also well-documented that women are more susceptible to stress-induced anxiety disorders than men. Corticotropin releasing factor (CRF) is a key regulator of the stress response exhibiting marked sex-dependent maturation during adolescence. The aim of the present study was to test if CRF hyper-signaling during adolescence alters anxiety-like traits and trauma susceptibility in adulthood, and hence, models long-term impact of early-life stress on the development of anxiety disorders. To test this hypothesis, we induced transient forebrain-specific CRF over-expression in male and female double mutant mice (Camk2a-rtta2 x tetO-Crf) during adolescence (postnatal days 23-44; CRFOEado) and assessed their anxiety-like traits (avoidance and startle reactivity) in adulthood following a single

traumatic event (predator exposure) or without stress exposure ('baseline anxiety'). We found that CRFOEado increased anxiety in females, but not males, assessed in three testing paradigms, i.e. open field, light-dark box and avoidance of predator-related cues. Although traumatic stress further increased anxiety levels in females, this effect was additive and did not interact with CRFOEado. Interestingly, CRFOEado did not result in startle hyper-reactivity which is in contrast to pre-adolescent CRFOE effects. These findings suggest that CRF hyper-signaling mediates long-term anxiogenic effects of early-life stress in a sex-dependent manner, which are also highly dependent on timing.

51. **CB1 receptor antagonism increases anxiety-like behavioural responses and alters neurochemical levels in two distinct populations of zebrafish.** Amanda Facciol1, Steven Tran2, Diptendu Chatterjee1, & Robert Gerlai1,2. 1University of Toronto Mississauga, Department of Psychology. 2University of Toronto, Department of Cell & Systems Biology. The function of the cannabinoid receptor type 1 (CB1-R) is poorly understood in zebrafish and numerous inconsistent findings have been reported in the literature. In the current study, we investigate the effect of CB1-R antagonism on anxiety-like behavioral responses, dopaminergic, and serotonergic responses in two distinct populations (AB and SF) of zebrafish. AB and SF zebrafish were treated with different concentrations of AM251 (0, 0.1, 1 mg/L), the CB1-R antagonist, and behavioral responses were quantified under two different contexts; following habituation and subsequently in a novel environment. The levels of dopamine, serotonin, and their metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA) were quantified from brain tissue using high precision liquid chromatography (HPLC). We found that a 60 minute exposure to AM251 (0, 0.1, 1 mg/L) did not alter behavioral performance following habituation in both populations. However, when subsequently transferred to a novel environment, zebrafish that were pre-treated with the highest dose of AM251 (1mg/L) exhibited increased anxiety-like behavioral responses including erratic movement, freezing, and bottom dwelling. Neurochemical analysis revealed that exposure to the highest dose of AM251 (1 mg/L) for 60 minutes increased whole-brain serotonin levels, independently of the type of population used. In contrast, exposure to 0.1 mg/L AM251 for 60 minutes decreased, whereas 1 mg/L AM251 increased whole-brain tissue levels of dopamine, DOPAC, 5-HIAA, independent of population. Our results reveal that blockade of CB1-Rs increases anxiety-like behavioral responses which is correlated with elevated whole-brain serotonin levels. In summary, our findings suggest that previous inconsistent findings regarding pharmacological blockade of CB1-Rs in zebrafish may be due to a combination of concentration and context-dependent effects. Funding: The research was funded by an NSERC Discovery Grant issued to Robert Gerlai.

52. **The Cacna1c genetic rat model for affective disorders: Behavioral phenotypes and inflammatory markers.** Braun, Moria D.1; Kisko, Theresa M.1; Kayumova, Rukshona1; Raithel, Clara1; Hohmeyer, Christine2; Rietschel, Marcella2; Witt, Stephanie H.2; Schwarting, Rainer K.W.1; Garn, Holger3; Wöhr, Markus1. 1 Behavioral Neuroscience, Faculty of Psychology, Philipps-University of Marburg, Gutenbergstraße 18, D-35032 Marburg, Germany. 2 Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, J5, D-68159 Mannheim, Germany. 3 Institute of Laboratory Medicine and Pathobiochemistry - Molecular Diagnostics, Faculty of Medicine, Philipps-University of Marburg, Hans-Meerwein-Straße 3, D-35043 Marburg, Germany. The neurobiological mechanisms ultimately resulting in the outbreak of affective disorders, i.e. major depressive disorder and bipolar disorder, are not fully elucidated yet. Genetic and environmental risk factors contribute critically to their etiology to varying degrees, but the exact pathophysiological pathways how these risk factors influence brain structure and function remain to be uncovered. Important genetic factors include the novel, yet well-established risk gene Cacna1c, while maltreatment and beneficial environment are among the most relevant environmental conditions that specifically act in windows of opportunity during early development. Here, we used the newly generated Cacna1c rat model to study its role in affective disorders. Firstly, behavioral phenotypes displayed by Cacna1c heterozygous (+/-) rats and wildtype littermate controls were compared in a sex-dependent manner. Secondly, Cacna1c +/- rats and wildtype littermate controls were exposed to post-weaning social isolation as a model for maltreatment or social plus physical enrichment to study the effects of beneficial environments on inflammatory markers. Our results show that Cacna1c +/-s rats are

viable, yet the average number of rat pups born per litter is smaller for Cacna1c +/- than for wildtype females, with genotypes being evenly distributed among the offspring. Interestingly, Cacna1c +/- females displayed less maternal licking and grooming behavior, while nursing behavior did not differ between genotypes. Consistent with the idea that low levels of maternal licking and grooming result in an anxious phenotype, offspring of Cacna1c +/- females emitted more isolation-induced ultrasonic vocalizations (USV) in the first week of life, as compared to offspring of wildtype females. In addition, Cacna1c +/- pups emitted fewer isolation-induced USV than wildtype littermate controls. No genotype differences were seen in body weight gain, body temperature regulation, and somatosensory reflexes, with both genotypes following a normal early developmental pattern. In adulthood, exploratory behavior in the open field was reduced in both male and female Cacan1c +/- rats. Finally, the measurement of cytokine levels revealed that post-weaning social isolation mostly increased proinflammatory markers, while social plus physical mainly led to opposite effects. Such changes were most prominently seen in wildtype littermate controls, with relatively minor environmental effects being evident in Cacna1c +/- rats. Together, our findings indicate that Cacna1c is involved in the regulation of behavioral phenotypes with relevance to neuropsychiatric disorders and that the responsivity to environmental changes at the level of inflammatory markers is reduced in Cacna1c +/- rats. Funding by Deutsche Forschungsgesellschaft (DFG), Project FOR 2107.

53. **The impact of maternal separation on adolescent social behavior may be mediated by changes in the maternal care after separation.** A. Magalhães (1), R. Alves (1), M. Nogueira (2), C.J. Alves (1), A. Mesquita (2), T. Summavielle(1), L. De Sousa (3). (1) Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal. (2) Centro de Investigação em Psicologia, Universidade do Minho, Portugal. (3) Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Portugal. Maternal care represents a critical environmental factor during early life and is known to have lasting effects on nervous system together with behavioral outcome later in life. We here examined the impact of short periods of early maternal separation (MS) on maternal behavior and how these events affect the development of social behavior during adolescence. MS paradigm was used not as a child negligent model but as a model of physical mother absence, an issue of major relevance in modern societies. A daily/2h mother–litter separation was performed from postnatal day (PND) 2-6 or from PND 10-14. Maternal care was evaluated after the end of the separation period, and social behavior was evaluated in the offspring during the adolescence period (PND 40-45). Behavior data were correlated with the expression profile of oxytocin receptor (OXTR) gene. Obtained results indicate that MS (2-6) has no effect on maternal behavior, however there was a significant effect of this MS period on the offspring social behavior, as showed by a decreased social affiliation/motivation and social novelty preference on adolescent rats, suggesting an inability to establish strong social bonds. In contrast, MS (10-14) have an impact on maternal behavior exhibited by an intensification of maternal affiliative behavior after reunion. Furthermore, the adolescent rat affiliative behavior was found to be increased after the same MS period (MS (10-14)), and was paralleled by an increased expression of OXTR in prefrontal cortex. Overall, our results reveal that short daily MS separation in early periods may be critical for mother-infant bonding quality and the impact of MS in the maternal care may be an underlying cause of critical repercussions on the social development. Supported by: FEDER founds through Programa Operacional Factores de Competitividade – COMPETE and Fundação para a Ciência e a Tecnologia, in the framework of the project ref. FCOMP-01-0124-FEDER-029576. Orçamento do Estado e FCT IF/00753/2014/CP1241/CT0005. FEDER founds through Programa Operacional Factores de Competitividade – COMPETE and Fundação para a Ciência e a Tecnologia, in the framework of the project PTDC/PSI-PCO/116612/2010, IF/01239/2014.

54. **Environmental enrichment prevents autistic-like behaviors following early life stress in CD-1 Mice.** Catherine Cornwell, Christopher Melton, Yoanna McDowell and Janelle LeMon. Department of Psychology, Syracuse University, Syracuse, NY. The maternal separation (MS) procedure has been used in rodents to model the effects of rearing human infants in environments that prevent normal bonding with a caretaker, such as orphanages or successive foster homes. It consists of removing infant

rodents from their nest and mother for 3 hours daily during the first 2 weeks of life, The present study examined whether MS impairs an appetitive social task in juvenile CD-1 mice, and if olfactory and/or cognitive changes might contribute to such impairment. It also determined whether peripubertal environmental enrichment (EE) would prevent these MS-induced changes. MS mice demonstrated reduced investigation of an enclosure containing a novel same-sex conspecific in a sociability task, impaired attraction to odors from their own, but not novel controls' nests, and failed to habituate to a familiar vs. novel object. EE prevented all three abnormalities. These results suggest that attentional, not sensory deficits, lead to social impairment after maternal separation and that environmental enrichment protects against this outcome. Analogous abnormalities have been associated with neurodevelopmental disorders in humans, most notably in autistic individuals. Our findings suggest that enrichment interventions may have merit for treating such disorders, as well as addressing the psychobiological consequences of early poverty. Supported by the Allport Undergraduate Research Fund of the Syracuse University Psychology Department.

55. **Nucleus incertus, GABA and relaxin-3: An emerging modulatory role in arousal, stress and memory.** Sherie Ma1,2, Giancarlo Allocca1,2, Emma EKE Ong-Palsson1,2; Caitlin E. Singleton1,2; Spencer J Williams3; Ross AD Bathgate1,2,4; Andrew L. Gundlach1,2,5. 1The Florey Institute of Neuroscience and Mental Health; and 2Florey Department of Neuroscience and Mental Health, 3School of Chemistry and Bio21 Molecular Science and Biotechnology Institute, 4Department of Biochemistry and Molecular Biology, 5Department of Anatomy and Neuroscience, The University of Melbourne, Victoria 3010, Australia. The nucleus incertus (NI) of the pontine periventricular grey consists of GABAergic neurons with long-range ascending projections to forebrain. Efferent and afferent connections implicate the NI in processes of 'behavioural planning, habenular function, hippocampal/cortical activity in attention/memory, and in oculomotor control'. The NI is a site of corticotropin-releasing factor (CRF) and orexin action, and forms a neural circuit positioned to modulate arousal and stress responses and the de/synchronization of hippocampal oscillatory theta (4-12 Hz) rhythm, prominent in the electroencephalograph (EEG) during exploration and memory processes. Theta rhythm underlies goal-oriented behaviour and cognition, and is a neurophysiological signature of REM sleep. The NI is also a primary site for neurons expressing the neuropeptide, relaxin-3, which can modulate septohippocampal activity and theta rhythm, and are associated with spatial working memory in the rat. However, NI function in awake, behaving animals remains unclear. Therefore, we used a pharmacogenetic approach (i.e. designer receptors exclusively activated by designer drugs, DREADDs) to modulate NI activity in freely-moving rats and assessed the behavioural and physiological consequences. An adeno-associated viral vector was used to transduce excitatory hM3Dq or inhibitory hM4Di into NI neurons of adult male rats. For behavioural and EEG recordings, DREADDs were activated by the designer ligand, clozapine-N-oxide (CNO). In hM3Dq-expressing rats, CNO activation of NI networks produced long-lasting theta activity, associated with increased locomotor activity and wakefulness, suggesting effects related to increased arousal and impairment of habituation and rest. Consistent with inactivation of the NI, hM4Di-expressing rats exhibited impaired spatial memory performance in the Morris water maze and Y maze. Current data suggest NI activity regulates behavioural state and I will review our findings on this emerging, integrative neural network associated with broad GABA/neuropeptide release, and its therapeutic potential.

56. **Pharmacotherapy combined with psychotherapy in social disturbances: plastic role of the ventromedial prefrontal cortex.** Eva Mikics*1, Nina Karpova*2, László Biró1, Ramon Guirado2, Christina Miskolczi1, Máté Tóth1, Diána Balázsfi1, Dóra Zelena1, Juzoh Umemori2, József Haller#1, Eero Castrén#2. 1Department of Behavioral Neurobiology, Institute of Experimental Medicine, Budapest, Hungary, 2Helsinki University, Neuroscience Center, Helsinki, Finland, *,# equal contribution. Aversive social environment during childhood including abuse and neglect is selectively associated with later antisociality and criminal behavior, however, the processes that mediate this relationship remain largely unknown. We have earlier demonstrated that post-weaning social isolation of rats – a laboratory modell for early social neglect – resulted in escalated and abnormal forms of aggressiveness and over-activation of several brain regions, including the medial prefrontal cortex (mPFC) during aggressive encounters in

laboratory rats. Deficits in prosocial behavior were eliminated by resocialization during adulthood, but abnormal aggression was resilient to this treatment. We assumed that escalated aggression was refractory to the corrective effects of re-socialization because of the adulthood-specific reduction in neural plasticity; therefore, here we investigated whether the neural plasticity-enhancer fluoxetine makes animals receptive to the effects of re-socialization in this model. The hypothesis was tested by combining psychosocial and plasticity-related pharmacological treatments (re-socialization and fluoxetine, respectively) in male rats submitted to post-weaning social isolation. According to our results, post-weaning social isolation induced abnormal and escalated forms of aggression in adulthood that was eliminated by the combination of 3-week long fluoxetine therapy and re-socialization, but neither treatment alone. To study treatment-induced changes in neural plasticity, we investigated gene expression profiles in brain regions relevant for aggression control by qPCR. Re-socialization and fluoxetine, albeit did have independent effects on neural plasticity in some brain regions, interactively modulated neural plasticity in the infralimbic cortex of the mPFC: the expression of BDNF 1 and 4, the epigenetic enzyme DNMT1 and aggression-related MAOA genes were down-regulated by post-weaning social isolation in the infralimbic cortex and restored by the combined but not by individual treatments. In summary, rats submitted to post-weaning social isolation model, fluoxetine dramatically enhanced the effects of re-socialization, indicating a synergistic interaction between positive social experiences and enhanced neural plasticity. The mPFC emerged as important mediator of the beneficial effect. This suggests that aggression problems may be solved by plasticity-related pharmacological treatments to promote the efficacy of psychotherapy.

57. **Altruistic behavior in rats is enhanced by experience.** Wrighten, Shayna; Kellis, Devin; Spears, Treonte. Department of Biology, Francis Marion University, Florence, SC, USA. Altruistic behaviors have long been studied in human and non-human primates, and for many years believed to only exist in these organisms. However, many findings suggest that rodents also carry out pro-social and altruistic behaviors. In order to further investigate altruistic behavior we examined this behavior using a rat model. To conduct these studies we used adult female rat pairs. One rat was placed into a restrainer that could only be opened from the outside (trapped rat). The restrainer was then placed into a larger enclosed area (arena) and her cagemate was placed inside the arena but outside the restrainer (free rat). The free rat could open the restrainer by pressing a lever holding the door closed. This paradigm, modified from that used by Bartal and colleagues, was designed to induce minimal social distress in the trapped rat in order to assess the altruistic behavior of her cagemate. The rats were placed in this paradigm for twenty trials, with one trial occurring each day for twenty minutes. After twenty trials the roles of the rats were reversed (newly trapped rat=experienced rat and newly free rat=naïve rat) and the experiment was repeated for another twenty trials. We found that a small percentage of naïve rats opened the door to release her cagemate, and that experienced rats were significantly more likely to open the door for her cagemate than were naïve rats. Control rats opened the door significantly less than did experienced rats. Control rats were placed into the restrainer for twenty trials (trials were the same as for pairs, except there was only one rat present for each trial) and then placed in the arena with the empty restrainer for twenty trials. We found a trend for a positive correlation between door opening behaviors within cagemate pairs, suggesting a trend for rats to be more likely to display altruistic behavior if first being the recipient of this behavior. Collectively, these data suggest that rats are more likely to engage in altruistic behavior if she has had previous experience the distressing environment and if she has first been the recipient of altruistic behavior. This paradigm provides a physically painless, mildly distressing way of studying the behavioral and neural aspects of altruistic behaviors in rats. Funding provided by SC INBRE grant and Francis Marion University.

58. **The Neural Correlates of Visual Imagery.** Winlove, Crawford I. P 1; Ranson, Jake 2; Aldworth, Susan 3; MacKisack, Matthew 1; Macpherson, Fiona 4; Onians, John 5; Zeman, Adam 1. 1. University of Exeter Medical School, UK. 2. St George's, University of London, UK. 3. University of York, UK. 4. University of Glasgow, UK. 5. University of East Anglia, UK. AIM: Visual imagery is a form of sensory imagination characterised by perception-like experiences in the absence of corresponding stimuli. Here, we report a co-ordinate-based meta-analysis of fMRI data that identifies the neural correlates of visual imagery. We will also share some initial results from the application of this method to the analysis motor imagery, and the protocol for a forthcoming study which will explore the neural basis of aphantasia: the absence of visual imagery. METHOD: Search terms were optimised using the Web of Knowledge and TAPoRware; calculations were performed using the Activation Likelihood Estimation algorithm (ALE, Turkeltaub 2012, implemented in GingerALE, v2.3.5), with a cluster-forming threshold of P=<0.001, and a cluster-level inference threshold of P=0.05 and 1000 repetitions. RESULTS: Searches identified 1554 papers on the 16th June 2015; on the basis of predetermined inclusion criteria, we extracted data from 45 papers, encompassing 762 foci and 510 participants. An overall comparison based on these studies identified 13 clusters of activation characteristic of visual imagery, within which there were 24 discrete foci. The largest clusters spanned contiguous areas of the left parietal lobule (encompassing BA7, BA40; 11,040mm3) and bilateral frontal areas (BA6; 6,552mm3). Other activations in prominently visual areas included the bilateral lingual gyrus (BA18), the right cuneus (BA17) and precuneus (BA7), and the bilateral fusiform gyrus (BA37). Finally, we found activation in the left claustrum, and both insulae. Differing patterns of activation were observed if the task required a decision based on the image, or accessed different memory systems. CONCLUSION: Visual imagery activates many of the same areas as visual perception, supporting a depictive interpretation for many of the underlying mental representations. Activity in other areas highlights the diversity of processes involved in the interpretation of these mental representations.

59. **Early-life inflammation decelerates fear extinction in adult rodents – Potential implications for the endocannabinoid system.** Doenni, Vienna M1; Hill, Matthew N1; Pittman Quentin J1. 1University of Calgary. Inflammation is one of the most common physiological stressors. While inflammation is a normal mechanism to clear pathogens, there is now emerging evidence that it can have substantial effects on development. In recent studies our lab discovered a susceptible window during which a single exposure to the bacterial endotoxin lipopolysaccharide (LPS) can cause long lasting changes in physiological and behavioral processes. To date the impact on anxiety related traits, substantially mediated by the amygdala, have not been determined. In the presented research we will address the hypothesis that a single postnatal LPS challenge causes long lasting alterations in amygdala-associated behaviors. It has previously been shown that general anxiety test such as open field behavior or behavior within an elevated plus maze are unaffected by P14 LPS. Early-life inflammation induced behavioral changes are more subtle and are frequently connected to behaviors know to be strongly mediated by endocannabinoids (e.g. social behavior or novelty induced suppression of feeding). Therefore we hypothesized that the extinction of a fearful memory cued by an auditory stimulus, a process highly dependent on amygdaloid cannabinoids, is altered (decelerated) by early-life inflammation. To that aim Sprague Dawley rats were bred in our facilities and treated on postnatal day (P) 14 with either 100µg/kg LPS or an equal volume of saline. On ~P60 animals were fear-conditioned to an auditory cue and subsequently subjected to a 2-day extinction protocol. Our experiments revealed delayed fear extinction on extinction day 1 in LPS injected animals in a repeated measure ANOVA design

(F (1,21) = 15.96, p < .01). Acquisition and reaction to the stimulus on day 2 were unaltered in P14 LPS treated animals. Due to the specific nature of the alteration and a previously established connection between P14 LPS and fatty acid amide hydrolase (FAAH) activity and endocannabinoid profiles in the amygdala, we hypothesized that by augmenting anandamide with a FAAH inhibitor (administered orally) we may be able to facilitate fear extinction in rats that experienced early-life inflammation. Our data indeed confirms this hypothesis, showing facilitation of fear extinction in P14 LPS injected animals but not controls. The findings in this study further elucidate the discussion about different predispositions to anxiety disorders such as posttraumatic stress disorder (PTSD). We believe that early-life inflammation plays a role in predisposing individuals to extended fear retention. Untangling the complicated mechanisms involved could yield the potential for more targeted therapies.

60. **SERT on speed: Enhanced emission of amphetamine-induced 50-kHz ultrasonic vocalizations in rats lacking the serotonin transporter due to long-term adaptations in 5-HT2C receptor functioning.** Kisko TM1, Willadsen M1, Vörckel KJ1, Seffer D1, Schwarting RKW1, Homberg J2, Wöhr M1. 1 Behavioral Neuroscience, Experimental and Biological Psychology, Philipps-University of Marburg, Gutenbergstr. 18, 35032 Marburg, Germany; 2 Behavioral Neurogenetics, Radboud University Medical Center, Stichting Katholieke Universiteit, Geert Grooteplein 21, 6525 EZ Nijmegen, The Netherlands. Rats emit calls in the ultrasonic range, so called ultrasonic vocalizations (USV). In appetitive situations, such as social play in juveniles or mating in adults, high-frequency 50-kHz USV occur. Notably, high-frequency 50-kHz USV are also seen in response to drugs of abuse, such as amphetamine (AMPH), and it is widely believed that in rats 50-kHz USV reflect a positive affective state, possibly associated with drug wanting and/or liking. We recently demonstrated that the neurotransmitter serotonin (5-HT) is strongly involved in the modulation of appetitive 50-kHz USV in response to AMPH. Specifically, we showed that 50-kHz USV emission can be completely blocked through the administration of the 5-HT2C receptor agonist CP809,101, while the 5-HT2C receptor antagonist SB242084 results in an enhancement in 50-kHz USV production, suggesting the 5-HT2C receptor as a pharmacological target for addictive disorders. Here, we show that rats lacking the serotonin transporter (SERT) emit more appetitive 50-kHz USV in response to systemic AMPH than heterozygous and wildtype littermate controls. AMPH-induced hyperactivity did not differ between genotypes. Moreover, deficits in pre-pulse inhibition following AMPH administration were seen irrespective of genotype. Thus, the effects of AMPH on sensorimotor functions appear not to be affected by the lack of SERT. This indicates that SERT is specifically involved in modulating the rewarding aspects of AMPH, with AMPH being more rewarding in SERT knockout rats. Importantly, the increase in appetitive 50-kHz USV is likely due to long-term changes in the 5-HT system, since 50-kHz USV emission following AMPH was not enhanced in wildtype controls when the selective 5-HT reuptake inhibitor escitalopram was co-administered. To identify relevant long-term changes in the 5-HT system, we targeted the 5-HT2C receptor and found that AMPH-induced behavioral alterations were not inhibited by the agonist CP809,101 in SERT knockout rats, while a clear inhibition was seen in heterozygous and wildtype littermate controls. In support of the specificity of the involvement of the 5-HT2C receptor, we further showed that the behavioral alterations induced by AMPH were potentiated by the antagonist SB242084 in controls but not in SERT knockout rats. Together, our findings indicate that SERT knockout rats display an enhanced emission of amphetamine-induced 50-kHz ultrasonic vocalizations due to long-term adaptations in 5-HT2C receptor functioning.

61. **Cortisol-signaling genes' DNA methylation changes due to early life stress assessed in peripheral tissues of adult male rhesus macaques.** Zsofia Nemoda1,*, Renaud Massart1, Matthew J. Suderman1, Angela M. Ruggiero2, Stephen J. Suomi2, Moshe Szyf1. 1 Department of Pharmacology and Therapeutics, McGill University, Montreal, Canada. 2 Laboratory of Comparative Ethology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA. *present address: Institute of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University, Budapest, Hungary. Increasing amount of research support that adverse social factors early in life affect stress reactivity, and are associated chronic diseases and mental health problems in humans. The broad range of health problems associated with early life stress (ELS) suggests a system-wide response, which is potentially mediated by epigenetic mechanisms, influencing stress reactivity, and the risk or resilience to develop diseases later in life. Animal studies present a crucial experimental design to disentangle the effects of the different environmental factors on key factors of the stress response systems. For example, low maternal care in rats induced long-lasting changes in the pups' DNA methylation level of the glucocorticoid receptor gene (NR3C1) in the hippocampus, which conferred higher stress reactivity in adulthood. Previous DNA methylation analyses showed ELS related changes in both prefrontal cortex and T lymphocytes of adult male rhesus monkeys (Macaca mulatta) subjected to parental deprivation. In this model mother-reared (MR) monkeys are raised by their biological mothers in social groups, whereas the surrogate peer-reared (SPR) monkeys are reared in a nursery during the first month, then in individual cages until 7 months of age. After this treatment period all animals are housed in large, peer groups. Our study aimed to assess the usability of easier accessible peripheral tissues, such as whole blood or non-invasively collected buccal swab samples. CD3+ T lymphocyte, whole blood and buccal cell samples of 2 year old rhesus males (5 MR vs 5 SPR) were analyzed by methylated DNA immunoprecipitation (MeDIP) coupled with promoter tiling arrays. Among the top common regulators of the overlapping differently methylated genes were NR3C1 and corticosterone, pointing to the altered methylation of genes from the stress response system. Validation of the array results were done by quantitative MeDIP and pyrosequencing. Higher methylation level of the NR3C1 gene was observed in the SPR group ($p<0.05$ at T lymphocyte and whole blood samples), similarly as it was shown before in brain samples. In addition, higher methylation of the corticotropin releasing hormone binding protein (CRHBP) gene was also detected in the SPR group compared to the control, MR group ($p<0.05$ for both blood and buccal samples). This study was supported by FP7-PEOPLE-2010-IOF N° 276107 Marie Curie International Outgoing Fellowship within the 7th European Community Framework Programme.

62. **Association between infant attachment behavior and DNA methylation of the glucocorticoid receptor gene promoter regions.** Emese Kruk1, Krisztina Lakatos2, Lívia Kende Őzéné2, Boglárka Bekecs2, Ildikó Tóth2, Judit Gervai2, Zsófia Nemoda1. 1 Institute of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University, Budapest, Hungary. 2 Institute of Cognitive Neuroscience and Psychology, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Budapest, Hungary. Inter-individual differences in stress reactivity have been linked to genetic and epigenetic variations in the hypothalamic-pituitary-adrenal (HPA) system, especially in the glucocorticoid receptor (NR3C1) gene. The fine-tuning of the HPA function during pre- and post-natal development has been in the center of stress-related studies, giving strong support for biological mechanisms of gene-environment interactions, including even in utero factors. Following model-building animal studies of maternal deprivation, findings from human studies also indicate the importance of DNA methylation

changes of the NR3C1 gene 1F promoter region in response to childhood maltreatment and suboptimal parental care both in hippocampus brain region and peripheral tissues, such as leukocytes. We hypothesized that normal variation in maternal behavior, especially anomalous maternal behavior can influence key regulatory elements, such as the NR3C1 gene in the infant. Since saliva samples have been successfully used in adults to assess stress reactivity by measuring cortisol levels and to evaluate DNA methylation differences of the NR3C1 gene promoters, we used this non-invasive sampling method in 100 one-year-old children assessed in the Strange Situation Test, measuring attachment behavior between infant and the primary caregiver, i.e. mother. Atypical maternal behavior was assessed by the AMBIANCE coding scheme focusing on affective communication errors. Because the NR3C1 gene has multiple alternative promoters (1B-G are expressed in hippocampus), we analyzed the DNA methylation levels of different NR3C1 gene promoter regions by pyrosequencing. There were significant differences in the DNA methylation level of the NR3C1 gene 1F promoter region at CpG-39 and CpG-42 in the salivary samples of infants with insecure attachment behavior compared to infants with secure attachment with DNA methylation being higher in the secure group for both loci (7.44% in the insecure vs. 8.61% in the secure group at CpG-39, p=0.016; and 3.13% vs. 3.87% at CpG-42, p=0.029). In these analyses we could not observe a mediator effect of the atypical maternal behavior. This study was supported by Hungarian OTKA fund K108882 and by Marie Curie International Outgoing Fellowship within the 7th European Community Framework Programme (FP7-PEOPLE-2010-IOF N° 276107).

Friday, June 10

8:00-10:00 ***Consequences of drugs and stress during adolescence: Today, Tomorrow, and Beyond.*** Chair: Elizabeth Byrnes; Co-Chair: Fair Vassoler.

The role of prefrontal norepinephrine in the ontogeny of cognitive control. Jill A. McGaughy1. 1University of New Hampshire. Corticopetal noradrenergic systems mature later than other neuromodulatory systems involved in cognitive control. Moreover prefrontal subregions seem to mature in an independent fashion with systems that confer resistance to distraction emerging before those critical to response inhibition. We assessed the impact of two standard medications to treat attention deficit disorder in a rodent model of cognitive control. We found low doses of atomoxetine, but not methylphenidate, improved cognitive rigidity in young adolescent rats. Young adolescent rats have a higher density of norepinephrine transporters (NET) in prelimbic cortex than older adolescent rats. This high density of NET is hypothesized to result in the cognitive rigidity by producing a functional deficit in norepinephrine that is corrected by low doses of atomoxetine. We also assessed the effects of a putative cognition enhancer, sodium butyrate, in adolescent rats. This drug exacerbated cognitive rigidity in adolescent subjects and was without benefit in other aspects of the task. These data will be discussed in the context of the impact of this drug on prefrontal circuits.

Nicotine-induced synaptic plasticity in the orbitofrontal cortex differ between adolescent and adult mice. Jill Turner1. 1University of South Carolina and the Medical University of South Carolina. More than 90% of adult smokers report their first use of tobacco before the age of 18. Smoking during adolescence increases the vulnerability to addiction and decrease the rate of successful quitting. Previous clinical studies have shown that adolescent rodents exhibited enhanced rewarding effects to nicotine. Considering the fact that enormous neurodevelopment occurs during adolescence, nicotine may differentially affect the brain at these two stages. We assess the impact of nicotine on long-term synaptic plasticity in the orbital frontal cortex (OFC), a brain region highly involved with impulse control, of

adolescent and adult mice. We found that in adolescent mice, a high-frequency tetanic stimulation protocol could successfully induce long-term potentiation (LTP) in the OFC. Upon nicotine bath application, the same stimulus paradigm induced sustained long-term depression (LTD). However, in adult mice, the same stimulation protocol failed to induce LTP; and nicotine failed to induce LTD either. The highly vulnarable synaptic plasticity in OFC during adolescence may underline their higher sensitivity to nicotine. These data will be discussed in the context of how nicotine differently affect the adolescent and adult brain and what potential consequences this may have for nicotine dependence. Work supported by the National Institutes of Health, NIDA grant 1-R00-DA032681.

Adolescent stress exposure increases vulnerability to addiction: Role of glutamate plasticity. 1Briand, L.A., 1Fosnocht, A.Q., 1Ellis, A.S., 1Deutschmann, A.U. 1Department of Psychology and Neuroscience Program, Temple University, Philadelphia, PA. Adolescence marks a key period of psychological and physiological development during which stressful experiences are poised to have a dramatic impact on future behavior. As such, adolescence marks a key period for vulnerability to current and future substance abuse. In particular, stress during adolescence, including low socioeconomic status, social isolation and chronic adverse life events, increases vulnerability to addiction. However, the underlying neurobiological mechanisms behind this vulnerability remain elusive. Therefore, the current studies utilized two adolescent stress paradigms in mice to determine their ability to modulate cocaine self-administration, extinction and reinstatement behavior. The first of these stressors was a social isolation stress in which mice were isolated at weaning, preventing adolescent social play behavior. While this stress exposure did not alter the acquisition of operant learning or fixed ratio cocaine self-administration during adulthood, isolated animals exhibited a greater motivation for cocaine, as evidenced by an increase in progressive ratio breakpoint as well as an increase in cue-induced cocaine seeking during reinstatement. Our second stressor, a 10-day chronic unpredictable stress paradigm, also led to an increase in motivation for cocaine during adulthood but the magnitude of this increase was not greater than that seen following isolation. We also examined the role of AMPA receptor trafficking in the ability of stress to modulate addictive phenotypes. We have evidence that disrupting the ability of activity-dependent AMPAR removal leads to an enhanced response to stress exposure following cocaine. Further, these mice exhibit increased cocaine taking following adolescent stress compared to wild type controls. These data will be discussed in relationship to how adolescent stress may affect the developing prefrontal cortex and this in turn may modulate future drug taking behavior.

A history of adolescent morphine exposure induces transgenerational effects on reward and relapse. Fair Vassoler1 1Tufts University Cummings School of Veterinary Medicine. Opiate use and abuse is devastating communities around the world. Often, initial opiate exposure occurs during adolescence, which represents a critical developmental window. Therefore, such drug exposure can have significant and lasting effects. Recently it has been proposed that drug use during adolescence may affect future offspring, even when drug use is discontinued prior to conception. Here we utilize a rodent model of adolescent opiate exposure. Male or female rats were exposed to either morphine or saline during adolescence. Following a prolonged period of abstinence, they were mated with drug-naïve animals. The offspring (F1 animals) were tested for morphine or cocaine self-administration, extinction, and reinstatement in adulthood. The data indicate that offspring from rats adolescently exposed to morphine (Mor-F1) have altered drug intake in a sex-, dose-, and parent-specific manner. This effect is also seen in the F2 generation. Together, the data tend to point towards increased sensitivity for opiates and cocaine and drug-specific changes in reinstatement behavior. RNA sequencing was utilized to look for potential gene expression changes that may underlie the observed effects. Genes involved in synaptic plasticity as well as myelin production and development were regulated in multiple generations. The data

will be discussed in the context of a novel mechanism for inheritance of drug addiction-related phenotypes. Funding for this work was from NIDA R01 DA025674, NIDA R03DA034886.

8:00-10:00 ***Selected topics of the Hungarian Behavioral Neuroscience.*** Chair: László Lénárd; Co-Chair: Robert Gerlai.

Substance P and neurotensin: Reinforcers in the limbic system. Lénárd L.1,2, László K.1, Kertes E.1, Ollmann T. 1, Péczely L.1, Kovács A. 1, Gálosi, R.1,, Karádi, Z.1,2 1Institute of Physiology, University of Pécs, Medical School, Pécs, Hungary, 2Molecular Neuroendocrinology and Neurophysiology Research Group, University of Pécs, Szentágothai Research Center, Pécs, Hungary. Experimental results indicate that substance P (SP) and neurotensin (NT) are involved in learning and memory processes. SP microinjections into the basal forebrain induce place preference with simultaneous increase of dopamine level, and NT has positive reinforcing effects after its direct microinjection into the ventral tegmental area. The roles of these neuropeptides have not been studied in other limbic structures, however. In the present experiments SP (10 or 100 ng), NK1 receptor antagonist WIN 51.708 (SP-ANT, 5.0 ng), NT (100 or 250 ng), NT1 receptor antagonist SR 48692 (NT-ANT, 35 ng) or dopamine D2 receptor antagonist sulpiride (4 µg) were microinjected into the central nucleus of amygdala (CeA), the ventral globus pallidus or into the ventral pallidum (VP) of Wistar rats. Antagonists were applied alone or 15 min prior neuropeptide microinjections. As behavioral paradigms place preference test (PPT), Morris water maze (MWM) and elevated plus maze test (EPT) were used. Lower dose of SP or NT resulted in place preference while after the higher dose only a tendency was observed. In the CeA, NT microinjections significantly reduced escape latency in the MWM. Lower dose of SP in the ventral globus pallidus and CeA caused anxiolytic effects. Similar anxiolytic effect was detected in the VP after NT microinjections while NT in the CeA was ineffective to modify anxiety. SP-ANT pretreatment prevented the effects of SP and NT-ANT antagonized the effects of NT. Dopamine D2 antagonist sulpiride pretreatment prevented the development of place preference and anxiolytic effects evoked by NT. Our results show that 1) SP and NT have strong reinforcing effects in the limbic structures observed, 2) In the CeA, NT microinjections improve spatial learning, 3) both SP and NT play important roles, though in different ways, in the development of anxiolysis, 4) The observed effects of SP are mediated via NK1 receptors while NT effects are due to NT1 receptor activation. Results observed after application of sulpiride clearly show the involvement of the dopamine system and the importance of dopamine-neuropeptide interaction in the reinforcing – learning mechanisms and in the regulation of anxiety.

The role of CRF and the urocortins in social interaction. Zsolt Bagosi, Krisztina Csabafi, Miklós Jászberényi, Gyula Telegdy. Department of Pathophysiology, Faculty of Medicine, University of Szeged, Hungary. Corticotropin-releasing factor (CRF) and the urocortins (UCN 1, UCN 2 and UCN 3) belong to the same CRF peptide family, having similar amino acidic structure, but different pharmacological properties. Besides their principle role in the regulation of the stress response, CRF and CRF-like peptides have been implicated in the social behavior of many species. The aim of the present study was to determine the role of CRF and the urocortins in the social interaction of mice. Male CFLP mice were administered intracerebroventricularly (ICV) CRF, UCN 1, UCN 2 or UCN 3 and then investigated in a Crawley social interaction test arena, which consists of three different chambers. Two types of tests were performed. In both types, first the tested male was habituated with the middle chamber of the arena for 5 minutes and then it was allowed to explore the remaining chambers for another 5 minutes, during which the number of entries and the time of interaction were measured. In the first test examining the sociability of mice, an unknown male was put in the first chamber, while the third chamber was left empty. In the second test examining the preference for social novelty of mice, a known female, with which the male was familiarized previously for 24 hours, and an unknown female were set in the opposite chambers. ICV injection of CRF reduced significantly the number of entries and the time of interaction with the unknown male. In addition, it also reduced significantly the number of entries and the time of interaction with the unknown female, but not the known female. ICV injection of UCN 1 increased significantly the number of entries into the chamber of the unknown male, without changing the time of interaction. In contrast, it

decreased considerably the number of entries into the chamber of both females, without changing the time of interaction. Central administration of UCN 2 and UCN 3 did not influence remarkably any of the parameters measured, except reducing the time of interaction between males. Our results demonstrate that CRF and UCN 1 play important, but different roles in the social interaction of mammals, which must be mediated by distinct receptors. Our results also suggest that UCN 2 and UCN 3 may be less relevant, but still involved in social behavior. The present study was sponsored by the Hungarian Brain Research Program and the Neuroscience Research Group of the Hungarian Academy.

Role of subcortical prefrontal projections in social behavior as revealed by axonal optic stimulation. Jozsef Haller1, Eva Mikics1, Laszlo Biro1, Eszter Sipos1, Dora Zelena1, Mate Toth1. 1Institute of Experimental Medicine of the Hungarian Academy of Sciences, Budapest, Hungary. We have shown earlier that about 20% of medial prefrontal (mPFC) neurons send projections to hypothalamic centers from where biting attacks can be elicited by electrical stimulation. Here we investigated the functional relevance of such projections by axonal optic stimulation of mPFC neurons in which channelrhodopsin-2 expression was induced by a viral vector. The optic stimulation of axons terminating in the mediobasal hypothalamus (MBH) reversibly increased the frequency of biting attacks delivered to opponents in a resident-intruder test. The optic stimulation of axons terminating in the lateral hypothalamus (LH) did not increase bite counts, but increased the share of attacks targeted on vulnerable body parts of opponents (head, throat and belly). The response was behaviorally specific. The overwhelming majority of hypothalamic axon terminals that originated from the mPFC were glutamatergic, and light pulses delivered at this level induced electric discharges in hypothalamic neurons. No retrograde activation was observed at the level of the mPFC. These findings show that biting attacks are controlled by two distinct prefrontal-hypothalamic projections: the mPFC-MBH projection controls the propensity to deliver bites, whereas the mPFC-LH projection controls attack targeting. These findings sharply contrast the prefrontal deficit theory of aggression, and reveal that bites are executed under the direct control of the mPFC.

Glucose-monitoring neurons in the medial orbitofrontal cortex of rat. István Szabó1, Edina Hormay1, Bettina Cseténvi1, Zoltán Karádi1,2. 1Institute of Physiology, Medical School, University of Pécs, Pécs, Hungary, 2Molecular Neuroendocrinology and Neurophysiology Research Group, Szentágothai Research Center, University of Pécs, Pécs, Hungary. The medial orbitofrontal cortex (mOBF) plays important role in the central regulation of feeding and metabolism. The glucose-monitoring (GM) neurons here have already been shown to be involved in these functions. In the present study, experiments with complex methodology were conducted to reveal multiple functional attributes of these chemosensory cells and to determine their homeostatic significance. In electrophysiological experiments, extracellular single neuron activity was recorded in anesthetized rats during 1) microelectrophoretic administration of chemicals, 2) intraoral gustatory, and 3) intragastric chemical stimulations. One fifth of the mOBF neurons proved to be elements of the forebrain GM neural network. Acetylcholine altered neuronal activity in 80%, whereas noradrenaline did so in 20%, and dopamine in 40% of all neurons. GABA inhibited a majority of the examined cells. Sweet taste stimulation changed the activity of one fourth of neurons, whereas one third did so in case of the sour taste. The other primary taste qualities and orange juice influenced the firing rate of appx. 60% of all neurons. Behavioral and metabolic tests were performed in awake rats after streptozotocin (STZ) induced selective destruction of the GM cells. No difference was found between the STZ treated and control groups in the acquisition capability of conditioned taste avoidance. In the taste reactivity (TR) tests, only minor difference was observed among the treated and the control animals, while in the acute glucose tolerance test (GTT), the maximum blood glucose concentration of the STZ treated rats appeared to be slightly higher, furthermore, dynamics of changes was also different in the two groups. When measuring plasma metabolite levels, minor shifts were found in the STZ microinjected but not in the control animals. Our findings demonstrate the existence of complex functional attributes of GM neurons in the mOBF. These chemosensory cells appear to play important role in the maintenance of homeostatic balance of the healthy organism. Supported by: Ajinomoto 51064/2009; PTE AOK KA 2013/34039/1.

The application of psychomotor vigilance measures in a nonhuman primate pharmacological model of neurocognitive disorders. Hernádi, István; Oláh, Vilmos; Trunk, Attila; Inkeller, Judit. Department of Experimental Neurobiology, Center for Neuroscience and Grastyán Translational Research Center, University of Pécs, Hungary. Age-associated pathological decline in cognitive function have become a major demographic health threat worldwide. Up to date, there are no effective pharmacological interventions against neurocognitive disorders such as Alzheimer's disease (AD). In order to develop a new pre-clinical disease model in non-human primates (NHP), here we implemented the 'reverse translational' approach. A modified version of the psychomotor vigilance task (PVT) was used to investigate similarities of cognitive function in healthy human volunteers and in adult rhesus macaques. We collected reaction time (RT) data to target stimuli and observed the effects of delay-related target expectancy on response speed in humans and in rhesus macaque NHPs. Then we induced transient cognitive decline by acute administration of muscarinic acetylcholine receptor antagonist scopolamine in the NHPs. The cholinesterase enzyme inhibitor donepezil was used to reverse acute adverse effects of scopolamine on cognitive performance. Results showed that both humans and NHPs exhibited similar target expectancy effects on RT, namely increasing fixation durations (delays) were followed by shorter RTs. In NHPs, scopolamine treatment resulted in decreased performance rate, increased RT and diminished target expectancy. Donepezil treatment significantly reversed impairments of task performance rate and RT, but did not reverse diminished target expectancy. Based on the present results we conclude that the PVT paradigm has high translational validity in it is suitable for both preclinical and clinical development of new potential therapeutic interventions against cognitive impairment and dementia.

Neural mechanisms for vocal social perception: dog-human comparative fMRI studies. Attila Andics1,2, Márta Gácsi2, Tamás Faragó2, Anna Gábor1, Dóra Szabó1, Ádám Miklósi1,2. 1Department of Ethology, Biological Institute, Eötvös Loránd University, 2MTA-ELTE Comparative Ethology Research Group, Eötvös Loránd University. Dog and human lineages split approximately 90-100 million years ago, but the two species have shared a similar social environment for the approximately 18-32 thousand years of domestication. This unique combination of evolutionary distance and shared environment, together with dogs' readiness to use human vocal social cues, puts dogs in a special position for comparative brain research. We developed methods to carry out functional magnetic resonance imaging tests in awake, unrestrained dogs and performed the first comparative fMRI studies of dogs and humans. This talk presents two experiments that explored what brain mechanisms dogs have in common with humans for speech processing. We found distinct, human-analogue neural correlates for discriminating speech sounds and speakers' voices (in the anterior cingulate cortex), and for processing word meaning and emotional prosody (in left and right non-primary auditory regions, respectively). These findings contribute to our understanding of how some specific components of the human linguistic capacity evolved. This research was supported by the Hungarian Academy of Sciences (Bolyai Scholarship to AA and F01/031 to MTA-ELTE Comparative Ethology Research Group) and the Hungarian Scientific Research Fund (OTKA K115862 and PD116181).

10:30 **Keynote Speaker:** Henriette van Praag, Neuroplasticity and Behavior Unit, Laboratory of Neurosciences, National Institute on Aging, Baltimore, MD.

Regulation and Function of Adult Hippocampal Neurogenesis: the Role of Exercise. Henriette van Praag. Neuroplasticity and Behavior Unit, Laboratory of Neurosciences, National Institute on Aging, Baltimore, MD. Most neurons in the adult central nervous system are terminally differentiated and cannot be replaced when they die. However, research over the past two decades has shown that small populations of new neurons are generated in the mature olfactory bulb and the hippocampus. In the adult hippocampus, newly born neurons originate from putative stem cells that exist in the subgranular zone of the dentate gyrus. The production, survival and functional integration of newborn hippocampal cells can be upregulated by voluntary exercise in a running wheel in rodents. Enhanced adult hippocampal neurogenesis is correlated with increased synaptic plasticity in the dentate gyrus, improved spatial navigation and pattern separation in rodents, indicating that adult-born hippocampal cells play a role in

cognition. These newly born neurons are an integral part of local intra-hippocampal circuits as well as more distal (sub)cortical networks. A recent focus of our research is to understand the functional contribution of the different structures that provide direct input to new neurons in the adult brain during the course of their development, as well as the reorganization of new neuron networks by exercise.

1:30-3:30 ***Current progress in characterizing therapeutic strategies and challenges after experimental CNS injury*****.** Chair: Anthony E. Kline; Co-Chair: Corina O. Bondi.

Unraveling frontal lobe dysfunction after TBI with pre-clinical models. Bondi, Corina1.2,3,4; Cooley, Emma1,3,4; Rohac, Rebecca1,3,4; Marshall, Ian1,3,4; McPeake, Emily1,3,4; Kutash, Lindsay1,3,4; LaPorte, Megan1,4; Cheng, Jeffrey1,4; Kline, Anthony1,3,4,5,6. 1Dept Physical Medicine and Rehabilitation, 2Dept Neurobiology, 3Center for Neuroscience, 4Safar Center for Resuscitation Research, 5Dept Psychology, 6Dept Critical Care Medicine, University of Pittsburgh. TBI models in the laboratory have been associated for decades with declines in long-term learning and memory, although the types of behavioral tests have not focused on the complex attention impairments related to the frontal lobe, which are common in most brain injuries. We have begun to employ the attentional set-shifting test (AST), a complex cognitive paradigm analogous to the Wisconsin Card Sorting Test, which is used to measure strategy-switching deficits in patients with frontal lobe damage, TBI, and psychiatric disorders. Previously, we demonstrated that a controlled cortical impact (CCI) injury to the parietal cortex produced significant impairments in executive function and cognitive flexibility in the AST. In one study to be presented, clinically relevant therapies for cognitive performance deficits after TBI are used alone and in combination, namely the enriched environment housing strategy and daily injections of the antidepressant drug citalopram, in order to mimic simultaneous rehabilitation and pharmacological treatments given to patients. Moreover, cognitive dysfunction in AST is also assessed in female rats post-injury, as females account for up to 45% of the TBI population. Considering that a large percentage of TBIs occur via direct impact to the frontal part of the skull (e.g., hitting windshield during an accident), we aimed to further assess higher-order cognitive impairments induced by a frontal TBI. Finally, the brain's ability to orchestrate biological responses such as activation of stress hormones or attentional focus is altered after TBI, thus cognitive dysfunction and depressive-like symptomatology may be augmented when persistent stress is present during the chronic phase of recovery. We are beginning to also investigate clinically-relevant cognitive-behavioral and anxiety-like dimensions sensitive to both TBI and chronic unpredictable stress. Additional studies to be presented will investigate specific brain pathways and mechanisms involved in mediating cognitive function after brain trauma. Supported, in part, by UPP/UPMC Academic Foundation (Corina O. Bondi, Ph.D.) and NIH grants NS060005, HD069620 and NS084967 (Anthony E. Kline, Ph.D.).

Using circuit-directed behavioral induction of immediate early genes as a biomarker for circuit integrity during recovery of brain injury. Theresa Currier Thomas1-3, Aida Khodadad2,4, P. David Adelson1,2, Jonathan Lifshitz1-3, 1BARROW Neurological Institute at Phoenix Children's Hospital-Phoenix, AZ. 2Child Health, University of Arizona College of Medicine – Phoenix, AZ. 3Phoenix VA Healthcare System- Phoenix, AZ. 4Neuroscience, University of Strasbourg, France. After experimental diffuse TBI, there is behavioral, structural and functional evidence that injured circuits are disrupted, then dismantled and eventually reorganized. A molecular biomarker of behavior-based circuit activation could elucidate disruption and concurrent impact of rehabilitative intervention on circuit integrity. Immediate early genes (IEG) are tightly coupled to activation in behavioral paradigms and could serve as a molecular marker of circuit activity to reveal the impact of behavior-based rehabilitation after TBI. In male SD rats (~325g), we have identified ARC as a potential IEG target, identified ARC's gene and protein expression time course after circuit stimulation and confirmed that our rehabilitation paradigm activates the targeted circuit. Ongoing experiments are assessing injury-induced changes in circuit activation and evaluating the impact of an early onset rehabilitation paradigm over time. Successful completion of these experiments would provide a foundation for assessing the structural and functional impact of type, timing

and onset of physical rehabilitation after TBI. Supported, in part, by NIH R03 NS077098, NIH R01 NS065052 and PCH Mission Support.

CRHR1 Mediation of neuroplasticity and neuroinflammation in the hippocampus following global cerebral ischemia. Authors: Patricia Barra de la Tremblaye1, PhD and Hélène Plamondon1, PhD. 1 Behavioural Neuroscience Group, Department of Psychology, University of Ottawa. Ischemic brain injury triggers restorative processes characterized by rapid neuronal growth and neuroplasticity, critical to optimize functional recovery of individuals post stroke. Brain-derived neurotrophic factor (BDNF) may be a promising avenue in the treatment of cerebral ischemic injury because this neurotrophin can enhance structural plasticity and cognitive performance. Mechanisms controlling release of BDNF are mediated by corticotrophin-releasing hormone (CRH) acting through its CRH type1 receptor in stressful conditions. However, whether CRH can mediate the release of BDNF in the reparative process triggered by ischemic injury remains to be characterized. Recently, we demonstrated that Antalarmin (ANT), a selective CRHR1 antagonist, can block the persistent neuroendocrine dysfunctions observed following global cerebral ischemia. In the study to be presented, we investigated the effect of ANT on the levels of BDNF and other plasticity markers, as well as on functional recovery after cerebral ischemia. Specifically, Male Wistar rats (N = 50) were subjected to sham surgery or global cerebral ischemia using the four vessel occlusion (4VO) model. ICV injection of ANT (2µg/2µl) or vehicle was administered 30 min prior to ischemia. Behavioural testing was initiated 7 days post ischemia and included assessment of anxiety and locomotor behavior in the elevated plus maze and open field, and fear and spatial learning in a Y-maze passive avoidance task and in the Barnes maze, respectively. Immunofluorescence served to detect BDNF and TrkB expression in the hippocampus, basal lateral amygdala (BLA), and the paraventricular nucleus of the hypothalamus (PVN) 30 days post reperfusion, and expression of markers association with neuronal injury and inflammation, including NeuN, glial fibrillary acidic protein (GFAP), ionized calcium binding adaptor (IBA1) and tumor necrosis factor α (TNFα). The data revealed improved spatial memory and fear retention in ANT-treated ischemic rats ($p < 0.01$). ANT also attenuated ischemia-induced increased and decreased BDNF and TrkB mRNA and protein levels in the amygdala and hippocampus, respectively ($p < 0.05$). The prolonged heightened BDNF and TrKB expression at the PVN also appeared influenced by CRHR1 signaling. ANT blunted post-ischemic IBA1, GFAP and TNFα-immunoreactivity in all hippocampal sub-regions and conferred neuronal protection in the CA1 and BLA ($p < 0.05$). Together, these findings suggest that CRHR1 activation upon cardiovascular insults significantly contributes to ensuing neuronal and functional changes influencing post ischemic recovery. This work was supported by a grant from the National Science and Engineering Research Council of Canada to Dr. Hélène Plamondon and internal funding from the University of Ottawa.

When behavioral management after brain trauma goes awry. Kline, Anthony E1-3,5,6, and Bondi, Corina O1,4-6, Departments of 1Physical Medicine & Rehabilitation, 2Psychology, 3Critical Care Medicine, 4Neurobiology, 5Safar Center for Resuscitation Research, 6Center for Neuroscience, University of Pittsburgh. Antipsychotic drugs (APDs) are often administered to TBI patients as a means of controlling agitation, albeit the rehabilitative consequences of this intervention are not well known. Hence, the goal of this presentation is to discuss the effects of APDs such as risperidone (RISP) and haloperidol (HAL) on behavioral outcome after experimental TBI. Studies assessing acute vs. chronic administration paradigms will be presented. Also discussed will be a study showing the long-term effects of a 3-week treatment paradigm with RISP and HAL. Lastly, data on the atypical APD aripiprazole and the benzodiazepine lorazepam will be presented as alternative approaches (to RISP and HAL) for controlling TBI-induced agitation without negative consequences.

1:30-3:30 ***The heterogeneity of depression: Obstacle or opportunity?*** Chair: Bill Deakin; Co-Chair: Gabriella Juhasz.

The role of comorbid disorders in deciphering the pathophysiology of depression. Gabriella Juhasz 1,2,3,4, Peter Marx 2,5, Peter Antal 2,5, Gyorgy Bagdy 2,3, Bill Deakin4. 1 MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group, Hungarian Academy of Sciences, Semmelweis

University, Hungary. 2 MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary. 3 Department of Pharmacodynamics, Faculty of Pharmacy, Semmelweis University, Budapest, Hungary. 4 Neuroscience and Psychiatry Unit, School of Community Based Medicine, Faculty of Medical and Human Sciences, The University of Manchester, UK and Manchester Academic Health Sciences Centre, UK. 5 Department of Measurement and Information Systems, Budapest University of Technology and Economics, Hungary. Major Depressive Disorder is a polygenic multi-factorial disorder. Despite the heterogeneous etiology the symptoms of depression in general are very similar. As a consequence it is extremely difficult to identify biologically distinct causal pathways. Instead, accumulating evidence suggests that overlapping or frequently comorbid disorders uniquely contribute to the pathomechanisms of depression. It has been demonstrated that many health conditions, such as other psychiatric disorders, syndromes accompanied with pain, or metabolic disorders increase the risk of depression and depression negatively affects the treatment outcome and the associated disability rate in these patients. Much less is known how vulnerability to depression is increased in these disorders. Network studies investigated different diseases and their symptoms suggests that overlapping symptoms between diagnostic categories determine the number of shared genetic risk factors and the extent to which their associated proteins interact. Thus, these common biological pathways in the face of environmental adversities, such as stress, sedentary lifestyle or unhealthy diet, may contribute to the development of comorbid disorders. Using the large cohort of the UK Biobank study we investigated which disorders are directly comorbid with depression and thus likely to share common biological mechanism. In addition, we explored the network of disorders that do not show direct comorbidity but are relevant for depression through other mediating medical conditions. Combining these disease networks with environmental factors, genetic and other biomarker data is a powerful tool to further our understanding of the pathophysiology of depression. This research has been conducted using the UK Biobank Resource. This work has been supported by the National Development Agency (KTIA_NAP_13-1-2013-0001), Hungarian Brain Research Program - Grant No. KTIA_13_NAP-A-II/14, by the Hungarian Academy of Sciences and the Hungarian Brain Research Program - Grant No. KTIA_NAP_13-2-2015-0001 (MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group), by the MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, Hungarian Academy of Sciences, Semmelweis University, and by the Manchester Academic Health Science Centre, University of Manchester.

Can we translate the diathesis-stress approach from animal to human research? Jaanus Harro1, Tanel Kaart2, Kariina Laas1, Toomas Veidebaum3. 1University of Tartu, 2Estonian University of Life Sciences, 3National Institute for Health Development. Depression develops in response to adverse life events and with higher probability in those individuals who have genetic predisposition. Animal models of depression have yielded a large variety of neurobiological responses to chronic stress. An analysis that used data across a variety of depression vulnerability and stress models has found that vulnerability is related to overall higher functional interconnectedness of regional activities in the brain as measured by oxidative metabolism (Harro et al. Behav Brain Res 2014, 267: 83-94). Brain-wise, chronic stress resulted in three different patterns of changes in oxidative metabolism. In absence of similar information in humans we have taken measures of subscales of major personality traits as proxys of persistent brain network state units and examined the interaction of occurrence of adverse life events with the 5-HTTLPR genotype as an index of depression vulnerability. Database of the longitudinal population-representative Estonian Children Personality Behaviour and Health Study (original n=1,238) was used, with life events recorded at age 15 and predicting personality scores at age 18 and 25. Personality traits differed very little between l/l homozygotes and s-allele carriers if the number of major adverse life events had been two or less. Higher levels of stress produced large shifts. Some of these were genotype dependent and others were not. Overall, subjects with the vulnerability genotype, the s-allele carriers, were more responsive to adverse life events, but the stress effect varied across personality facets. Aspects of neuroticism were affected most consistently, and if summed were increased only in s-allele carriers. Nevertheless, Anger and Immoderation were most sensitive to stress, and rather reduced in l/l homozygotes. Especially the Anxiety facet, but also Depression and Self-Consciousness were increased

by stress independently of genotype. Facets of Extravesion were generally reduced by stress but Gregariousness was reduced in s-allele carriers and Excitement-Seeking in l/l homozygotes. Of the facets of agreeableness, Morality was reduced by stress in s-allele carriers while Cooperation was rather increased in l/l homozygotes. Cautiuosness was reduced in s-allele carriers and increased in l/l homozygotes. In summary, these findings suggest that adverse life events do not impact on the psychopathological mechanisms leading to depression directly and in a uniform manner but rather produce a complex modification of traits and their underlying neurobiological processes that, dependent on aspects of vulnerability as promoted by gene variants, in the course of time bring about the clinically relevant depressive state but with heterogenous symptomatology. This work was supported by the Hope for Depression Research Foundation and the Institute for the Study of Affective Neuroscience, the EC 6FP Integrated Project NEWMOOD, the EC 7FP Collaborative Project Aggressotype, and the Estonian Ministry of Education and Science project IUT20-40.1.

Stratification of Appetite Changes in Depression and in Response to Anorectic Drugs using functional Magnetic Resonance Imaging. Colin T Dourish. P1vital, Manor House, Howbery Park, Wallingford, Oxfordshire OX10 8BA, UK. The incidence of depression is growing and the WHO estimates that depression affects 350 million people worldwide. Similarly, the worldwide incidence of obesity has soared from 12% to 19% since 1995 and it is estimated that 1 in 5 of the world's population is obese. A meta-analysis identified a reciprocal link between depression and obesity showing that obesity increased the risk of depression and depression was predictive of developing obesity. However, increased appetite and obesity are not apparent in all patients with depression. Thus, patients exhibit marked heterogeneity in appetite, with 48% reporting depression-related decreases in appetite whereas 35% have depression related increases in appetite. Similarly, there are considerable individual differences in response to drugs used to treat obesity as some patients experience substantial reductions in appetite and body weight whereas others show little or no response. Recent functional Magnetic Resonance Imaging (fMRI) studies suggest it may be possible to stratify patients with depression who show increased and decreased appetite and individuals who respond or fail to respond to a serotonergic appetite suppressant on the basis of changes in the brain's reward circuits to food stimuli. In patients with depression with increased appetite greater responses to food pictures than patients with depression and decreased appetite were observed in key reward areas including orbitofrontal cortex and insula. Depressed patients with increased appetite also had elevated activity compared to both healthy controls and depressed patients with decreased appetite in ventral striatum, putamen and ventral pallidum. The 5-HT2C receptor agonist meta-chlorophenylpiperazine (mCPP) decreases food intake in lean and obese volunteers and has a greater effect on the intake of a palatable high calorie snack (cookies) than a low calorie pasta lunch. It was possible to classify participants into two groups (drug responders and non-responders) based on cookie intake after mCPP. Non-responders rated the cookies as more pleasant than responders in the absence of differences in hunger or pasta consumed during lunch. Non-responders exhibited greater activity than responders in key reward areas including orbitofrontal cortex and dorsomedial prefrontal cortex to high calorie food images. These findings could explain bidirectional changes in appetite in patients with depression and individual variability in responses to serotonergic anti-obesity drugs. Differences in brain activity to food may be useful as biomarkers of depression subgroups and help to develop new treatments for both depression and co-morbid obesity. Furthermore, it may be possible in clinical trials of novel compounds and in clinical practice to identify individuals who are more likely to respond to certain types of medication, leading to stratified and more effective treatments.

Exploring possible stratifications using a Bayesian systems-based approach in large-scale heterogeneous data. Gabor Hullam 1,2, Gabriella Juhasz 2,3,4,5,Peter Antal 1,2. 1 Department of Measurement and Information Systems, Budapest University of Technology and Economics, Hungary. 2 MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary. 3 MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group, Hungarian Academy of Sciences, Semmelweis University, Hungary. 4 Department of Pharmacodynamics, Faculty of Pharmacy, Semmelweis University, Budapest, Hungary. 5 Neuroscience and Psychiatry Unit, School of Community Based Medicine, Faculty of Medical and Human

Sciences, The University of Manchester, UK and Manchester Academic Health Sciences Centre, UK. Understanding the mechanisms of multifactorial traits such as depression requires the capability of creating complex models which include environmental factors, life stressors, co-morbid conditions, and genetic variables. In order to explore such complex relationships and their connection with additional epidemiologic and lifestyle variables and clinical descriptors a systems-based modelling approach is needed which allows the representation of multivariate dependency patterns. One possible solution is to use Bayesian systems-based methodology which provides the means to analyze the relevance of factors with respect to multiple phenotypes and to infer corresponding causal models. In addition, the underlying Bayesian statistical framework provides a consistent, multivariate measure of relevance that is applicable in case of high-dimensional, heterogeneous data. However, the highly interdependent and interacting nature of environmental factors, co-morbid phenotypes and other risk variables poses a considerable challenge for detecting relatively weak effects of factors, such as genetic effects in case of depression phenotypes. The identification of such effects may depend on finding an appropriate context, i.e. a stratum, in which the relationship with the target phenotypes is detectable. Such contextual relationships make up a significant proportion of the mechanisms of complex traits thus making stratification a priority. Furthermore, stratification may also lead to the definition of novel complex phenotypes that enhance the detection of a complex trait. We will explore possible stratification strategies based on the Bayesian systems-based methodology using a large-scale data related to depression phenotypes. This research has been conducted using the UK Biobank Resource. This work has been supported by the National Development Agency (KTIA_NAP_13-1-2013-0001), Hungarian Brain Research Program - Grant No. KTIA_13_NAP-A-II/14, by the Hungarian Academy of Sciences and the Hungarian Brain Research Program - Grant No. KTIA_NAP_13-2-2015-0001 (MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group), and by MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, Hungarian Academy of Sciences, Semmelweis University.

4:00-5:00 ***The different faces of hippocampal theta.*** Chair: Colin Lever.

Spatial cognition or Anxiety? Can dissociable theta frequency correlates reconcile opposing views of hippocampal function? Colin Lever, Miranda Hines, Steven Poulter, Vincent Douchamps, Anthony McGregor. University of Durham, U.K. The primary function of the hippocampus is much debated. Interestingly, despite divergent theoretical views of the hippcampus' main function, the theta oscillation plays a central role in all of these theories. For instance, the 'spatial cognition and memory' hippocampus school (e.g. see O'Keefe and Nadel, 1978, The hippocampus as a cognitive map) can point to positive correlations between theta frequency and speed of locomotion, likely linked to theta-modulated speed cells in entorhinal cortex and other spatial cells showing linear rate-speed relationships, all suggesting a role for theta in path integration. The 'anxiety' hippocampus school (e.g. Gray, 1982, The neuropsychology of anxiety) can point to the result that all tested anxiolytic drugs (e.g. 5HT1A agonists, benzodiazepines, SSRIs) reduce the frequency of reticular-elicited hippocampal theta, despite acting on very different primary targets. We present studies from our lab supporting a model (Burgess, 2008, Hippocampus; Wells et al, 2013, Journal of Neuroscience) which suggests that there are two simultaneous additive contributions to hippocampal theta frequency. The first is a spatial cognition component, and is described by the slope of the relationship between theta frequency and speed of locomotion. We show that this slope variable is linked to spatial context novelty, and spatial novelty-dependent behaviour. The second is an arousal/anxiety-sensitive component, and is described by the 0cm/s intercept that the theta frequency vs speed regression line makes upon the theta frequency axis. We show that this component of theta frequency is reduced by the systemic administration of anxiolytic drugs. We test Pregabalin, a presynaptically-acting □2-□ calcium-channel blocker and anti-epileptic which is also an effective anxiolytic drug licensed for anxiolysis in the EU. As our model predicts for an anxiolytic drug, pregabalin specifically reduces the intercept component of theta frequency. In contrast, Lamotrigine, also an anti-epileptic drug, but not an anxiolytic, does not reduce this intercept. Our results offer a new physiological perspective upon dual hippocampal functionality, potentially reconciling ostensibly rather different views of hippocampal function.

Coding of space and time by interactions of entorhinal cortex and medial septum. Michael Hasselmo, Boston University. Neurophysiological data demonstrates neural responses in entorhinal cortex and hippocampus that may code space and time for memory guided behavior. These responses include the coding of spatial dimensions of behavior by grid cells (Moser and Moser, 2008), place cells (O'Keefe and Burgess, 2005), and boundary cells (Lever et al., 2009), and the coding of temporal dimensions by time cells (Kraus et al., 2013; 2015). Manipulations of medial septal modulation influence network oscillatory dynamics (Wells et al., 2013) as well as the entorhinal coding of space (Brandon et al., 2011) and time (Wang et al., 2014). These effects on the coding of space and time may involve modulation of cellular mechanisms of resonance and rebound spiking (Giocomo et al., 2007; Shay et al., 2015) and persistent spiking (Yoshida et al., 2013; Tiganj et al., 2015). Models demonstrate how intrinsic properties may contribute to coding of space and time, while addressing data on spiking activity showing theta phase precession and theta cycle skipping (Brandon et al., 2013). Modeling has also addressed the potential mechanism of influence of visual stimuli on grid cells (Raudies et al., 2012) and the role of grid cells in goal-directed spatial navigation (Erdem and Hasselmo, 2014).

What does hippocampus tell hypothalamus? Optogenetic control of hippocampal theta oscillations reveals their function in locomotion. Bender, Franziska1,2, Gorbati, Maria1,2, Carus-Cadavieco, Marta1,2, Denisova, Natalia1,2, Gao, Xiaojie1,2, Holman, Constance1,2, Ponomarenko, Alexey1,2, Korotkova, Tatiana1,2. 1Leibniz Institute for Molecular Pharmacology, Berlin, Germany; 2NeuroCure Cluster of Excellence, Berlin, Germany. Hippocampal theta oscillations support encoding of an animal's position during spatial navigation, yet longstanding questions about their impact on locomotion remain unanswered. Combining optogenetic control of hippocampal theta oscillations with electrophysiological recordings in mice, we found that hippocampal theta oscillations causally affect locomotion. We identified that their regularity underlies more stable and slower running speed during exploration. More regular theta oscillations were accompanied by more regular theta-rhythmic output of pyramidal cells. Theta oscillations were coordinated between hippocampus and its main subcortical output, the lateral septum (LS). Inhibition of this pathway, using chemo- (DREADDs) or optogenetics (halorhodopsin, eNpHR3.0), revealed its necessity for the hippocampal control of running speed. Theta-rhythmic optogenetic stimulation of ChETA-expressing LS projections to the lateral hypothalamus replicated the reduction of running speed induced by more regular hippocampal theta oscillations. These results suggest that changes of hippocampal theta synchronization are translated via the LS into rapid adjustment of locomotion. The present study shows that movement-dependent bottom-up modulation from subcortical regions to hippocampus is complemented by the top-down feedback, signaled by hippocampus to locomotor circuits. Our findings further suggest that hippocampal theta-rhythmic signaling is read out in parallel by cortical and subcortical regions, rapidly regulating exploratory activity according to representations of environment. We gratefully acknowledge support by The Human Frontier Science Program (HFSP; RGY0076/2012, TK), DFG (Exc 257 NeuroCure, TK and AP, SPP1665, AP) and GIF (I-1326-421.13/2015, TK).

Theta-related physiology in the freely moving developing rat. Thomas J Wills1 1University College London, London. During post-natal development, the hippocampal theta rhythm is present from the earliest ages that rats commence movement and exploration. We recorded local-field potentials and extracellular spiking in the hippocampal CA1 field of freely moving rats, from the first emergence of exploration onwards, between the ages of postnatal day 14 and 30 (P14 – P30). We confirmed previous findings from immobile and sleeping rats that theta frequency increases with age, from rising approximately 4-5Hz to 8Hz between P14 and P30. We further characterised the rhythmicity of CA1 pyramidal spiking with respect to theta, finding that both the degree of theta modulation, and the preferred theta phase of spiking, change during the pre-weanling period (P14-P21). Finally, we tested whether theta frequency is reduced during exposure to a novel environment (proposed to be a network signal for novelty, in adult rats). We found that novelty-dependent theta frequency reductions were observed in young rats, but that there was a dissociation between the environmental manipulations that evoked frequency reduction, in young rats and in adults.

4:00-5:00 ***Role of the prefrontal cortex and hippocampus in motivation, decision making, and drug relapse: Cooperation or competition?*** Chair: Jennifer M. Bossert.

My ERK-some PFC: A glutamatergic basis for incubated drug-craving. Karen K. Szumlinski1.1University of California Santa Barbara. A diagnostic criterion for drug addiction, persistent drug-craving continues to be the most treatment-unmanageable aspect of addiction that maintains the chronic, relapsing, nature of this disease. Despite the high prevalence of psychomotor stimulant addiction, there currently exists no FDA-approved medication for craving cessation, owing, in good part, to our lack of understanding of the neurobiological underpinnings of drug craving. In humans, cue-elicited drug-craving is associated with the hyper-excitability of prefrontal cortical regions. Using a rodent model of cocaine addiction, my laboratory has characterized how a history of excessive cocaine-taking impacts excitatory glutamate signaling within the prefrontal cortex to drive drug-seeking behavior during protracted withdrawal. This presentation will provide evidence that the capacity of drug-associated cues to augment craving in highly drug-experienced animals relates to an incubation of glutamate release within prelimbic cortex, present a theoretical molecular model to account for persistent drug-craving and discuss the potential for existing, FDA-approved, chemotherapeutics agents as a novel approach to craving intervention in cocaine addiction.

Role of projections from ventral subiculum to nucleus accumbens shell in context-induced reinstatement of heroin seeking in rats. Jennifer M. Bossert1, Sweta Adhikary1, Robyn St. Laurent1, Nathan J. Marchant1,2, Hui-Ling Wang3, Marisela Morales3, Yavin Shaham1. 1 Behavioral Neuroscience Branch, IRP-NIDA, NIH. 2 Florey Institute of Neuroscience & Mental Health, University of Melbourne. 3 Integrative Neuroscience Branch, IRP-NIDA, NIH. Rationale and objective: In humans, exposure to contexts previously associated with heroin use can provoke relapse. In rats, exposure to heroin-paired contexts after extinction of drug-reinforced responding in different contexts reinstates heroin seeking. We previously demonstrated that the projections from ventral medial prefrontal cortex (vmPFC) to nucleus accumbens (NAc) shell play a role in this reinstatement. The ventral subiculum (vSub) sends glutamate projections to NAc shell and vmPFC. Here, we determined whether these projections contribute to context-induced reinstatement. Methods: We trained rats to self-administer heroin (0.05-0.1 mg/kg/infusion) for 3 h per day for 12 days; drug infusions were paired with a discrete tone-light cue. Lever pressing in the presence of the discrete cue was subsequently extinguished in a different context. We then tested the rats for reinstatement in the heroin- and extinction-associated contexts under extinction conditions. We combined Fos with the retrograde tracer Fluoro-Gold (FG) to determine projection-specific activation during the context-induced reinstatement tests. We also used anatomical disconnection procedures to determine whether the vSub→NAc shell and vSub→vmPFC projections are functionally involved in this reinstatement. Results: Exposure to the heroin but not the extinction context reinstated lever pressing. Context-induced reinstatement of heroin seeking was associated with increased Fos expression in vSub neurons, including those projecting to NAc shell and vmPFC. However, anatomical disconnection of the vSub→NAc shell projection, but not the vSub→vmPFC projection, decreased this reinstatement. Conclusions: Our data indicate that the vSub→NAc shell glutamatergic projection, but not the vSub→vmPFC projection, contributes to context-induced reinstatement of heroin seeking. Support provided by NIDA IRP.

Prefrontal cortex and hippocampus: Henchmen of addiction. Fuchs, Rita A1. 1Washington State University College of Veterinary Medicine, Department of Integrative Physiology and Neuroscience, Pullman, Washington, USA. The prefrontal cortex is a functionally heterogeneous brain region with executive functions that encompass the assessment of reward value, decision making, response selection, and the initiation of complex goal-directed behaviors. Accordingly, studies from our laboratory have shown that, within the prefrontal cortex, the orbitofrontal cortex plays a requisite role in drug context-induced impulsive decision making and the dorsomedial prefrontal cortex regulates the expression of drug context-induced cocaine-seeking behavior. Unlike the prefrontal cortex, the hippocampal formation is a canonical brain region in learning and memory. Furthermore, its contributions to drug addiction-related phenomena have been underappreciated. Studies from our laboratory have established that the

dorsal hippocampus critically contributes to the ability of drug-associated environmental stimuli to trigger drug-seeking behavior in rats by supporting the reconsolidation of labile drug-related contextual memories and by mediating the retrieval and or utilization of established drug-related contextual memories. This symposium presentation will review these and additional studies that provide insight into the pharmacological and cellular mechanisms by which the hippocampus and prefrontal cortex support maladaptive associative memories and cognitive strategies, respectively, that perpetuate addictive behavior. This work was supported by National Institutes of Health/National Institute on Drug Abuse grants R01 DA025646, R01 DA017673, and R21 DA036660.

Hippocampal circuits in cognition and behaviour. Yogita Chudasama. National Institute of Mental Health, Bethesda, MD 20892, USA. In rats, the most studied aspects of hippocampal function relate to its role in spatial learning and memory. However, the complexity of its anatomical connections, the effects of selective hippocampal lesions, and electrophysiological activity in behaving animals have made it clear that its role in cognition is much more comprehensive. In this talk, I will review some of our recent experimental findings that shed light on the hippocampus in cognition and behavior. I will focus on the hippocampus and its interactions with the prefrontal cortex and midline thalamus. I will illustrate how some features of hippocampal lesions resemble the effects of prefrontal lesions such as in aspects of behavioral control. In other cases, I'll report features that distinguish them such as in decision making. Most notably, I'll show how midline thalamic lesions enhance cognitive performance along several dimensions that would normally be impaired following prefrontal or hippocampal lesions.

5:00-6:00 ***Oral Session 3. Learning, Memory, Attention, and Related Cognitive Functions.***

In vivo optogenetic manipulation of dopamine neurons in a novel behavioral economics based food-seeking task. Erik B. Oleson1, Katherine Pultorak1, Gregory Krzystyniak1, Raibatak Das1, Scott Schelp1. 1University of Colorado Denver. The mesolimbic dopamine system is strongly implicated in motivational processes. Currently accepted theories suggest that transient mesolimbic dopamine release events are involved in assessing the value of reward predictive stimuli and/or in generating motivated action sequences directed toward obtaining reward. During the pursuit of reward, critical associations are formed between the reward and otherwise neutral stimuli that begin to predict reward availability. Through these experiences, dopamine neurons, which initially represent the receipt of reward, begin to represent its earliest conditioned predictor (i.e., cue). The resulting concentration of dopamine release scales proportionally to the magnitude of reward predicted. Here, we are investigating the role of cue- and reward-evoked dopamine release on cue-motivated food seeking. To address this research question we developed a novel behavioral economics food-seeking task. In this task, food is provided to rats across 10 different unit-prices (i.e., response requirement/reward magnitude). Importantly, in this task, multiple pairings (>10/price/session; unlike with progressive ratio schedule) occur between each unit-price, reward and its predictive cue. Using fast-scan cyclic voltammetry we first determined that the concentration of accumbal dopamine time-locked to cue presentation decreases as a function of unit-price in this task. We next sought to assess the effect of optically augmenting release both at reward delivery and cue presentation. We selectively activated channelrhodopsin-2 expressing dopamine neurons within the ventral tegmentum during either cue or reward presentation (order counter balanced across animals). Preliminary data reveal that optically facilitating dopamine release at the cue decreases motivation for food; whereas, facilitating release at reward delivery increases motivation for food. Interestingly, optically augmenting release at both cue presentation and reward delivery decreased response latency, consistent with an invigoration of responding that might be dissociable from value-based changes in motivation. It is possible that augmenting cue-evoked dopamine release decreases motivation in our task because we are violating the animal's expectation (i.e., the animal receives less than expected) and vice versa. Together these findings suggest that cue- and reward-evoked dopamine release play a causal role in action initiation, yet oppositely influence motivation in value-based behavioral economics based tasks.

ERK phosphorylation of cholinergic medial septal neurons by icv infusión of a relaxin3 agonist impairs spatial working memory. Francisco E. Olucha-Bordonau1, Héctor Albert-Gascó1, Álvaro

García-Avilés1, Salma Moustafa1, Sandra Sánchez-Sarasua1, Andrew L. Gundlach2,3, Ana M. Sánchez-Pérez1. 1Department of Medicine, School of Medical Sciences, University Jaume I, 12071 Castellón de la Plana, Spain. 2The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria 3052, Australia. 3Florey Department of Neuroscience and Mental Health, The University of Melbourne, Victoria 3010, Australia. The medial septum/diagonal band (MS/DB) is a relay region connecting the brainstem with the hippocampus, and both the MS/DB and dorsal/ventral hippocampus receive strong topographic GABA/peptidergic projections from the nucleus incertus of the pontine tegmentum. The neuropeptide relaxin-3, released by these neurons, is the cognate ligand for a Gi/o-protein-coupled receptor, RXFP3, which is highly expressed within the MS/DB, and both cholinergic and GABAergic neurons in this region of rat brain receive relaxin-3 positive terminals/boutons. Comprehensive in vitro studies have demonstrated that a range of cell signaling pathways can be altered by RXFP3 stimulation, including inhibition of forskolin-activated cAMP levels and activation of ERK phosphorylation. In this study we investigated whether intracerebroventricular (icv) injection of RXFP3-A2, a selective relaxin-3 receptor agonist, altered ERK phosphorylation levels in the MS/DB of adult male rats. In addition, we assessed the neurochemical phenotype of phosphorylated (p) ERK-positive neurons in MS/DB after RXFP3-A2 administration by dual-label immunostaining for pERK and key neuronal markers. RXFP3-A2 injection significantly increased pERK levels in MS/DB, compared to vehicle at 20 and 90 min post-injection. In addition, icv injection of RXFP3-A2 increased the number of cells expressing pERK in the MS/DB after 90 min, with increases detected in cholinergic, but not GABAergic neurons and RXFP3 distribution greatly overlays that of cholinergic neurons at the MS/DB. Furthermore, infusions of RXFP3-A2 caused an impairment of memory consolidation of “spontaneous altenation” in a T-maze delayed paradigm. The specific RXFP3-related activation of the MAPK/ERK pathway in MS/DB cholinergic neurons identifies them as a key target of ascending relaxin-3 projections, with implications for the acute and chronic regulation of cholinergic neuron activity/function by relaxin-3/RXFP3 signaling under normal physiological conditions and in pathological disorders. This research was supported by FPI-UJI: PREDOC/2014/35, FP7-PEOPLE-IRSES PIRSES-GA-2012-318997 NEUREN, NHMRC (Australia) (1027522, 1026939), Generalitat Valenciana (AICO/2015/042) and Universitat JaumeI (P1·1A2014-06).

The Aid of Ephedrine HCL, Curcumin and Turmerone in Neurogenesis and Inhibition of Beta-Amyloid Plaques in Transgenic Mice Models. Dr.Keerthi Paramasivam. King’s College London, WC2R 2LS, United Kingdom. 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.

The sound of silence - The role of vocalizations in sociosexual behaviors and mate choice in groups of rats (Rattus Norvegicus) in a seminatural environment. Xi Chu1, Anders Ågmo1. 1University of Tromsø, Norway. Both male and female rats produce vocalizations in the presence of a potential sexual partner. In this study we evaluated the role of vocalizations in sociosexual behaviors in

an ecologically valid procedure. Groups of rats (3 males and 4 receptive females) were housed in a seminatural environment. One part of the environment consisted of a series of tunnels and small chambers similar to a natural rat burrow. This part was lit by infrared lamps and connected to a large open area illuminated on a 12:12 hr light/dark schedule. Water and food were available in the open area. In each group one or two males and two females were devocalized and the other subjects were sham operated. All females were ovariectomized and brought into behavioral estrus by a subcutaneous injection of estradiol benzoate, 18 µg/kg per rat, followed by progesterone, 1 mg/kg per rat, approximately 48 h and 3–4 h before observation, respectively. The subjects were allowed to explore in this environment undisturbed for 5 days before the injection. Sociosexual interactions between males and females were recorded for a period of one hour when all four females were receptive. This means that sociosexual interactions were recorded only when the males had the choice to interact either with vocalizing or with silent females. Devocalized and sham operated males displayed very similar behavioral patterns towards the females regardless of whether the females were devocalized or not. There was no difference in any of the male sexual behavior patterns nor in male-initiated non-sexual social interaction. This suggests that female vocalizations do not contribute to the regulation of sociosexual interaction. Likewise, devocalized males received as much attention from females as sham operated males, with the exception of paracopulatory behavior (female approaching a male followed by runaway, often associated with hops, darts, and ear wiggling) which were more frequently directed towards the sham operated males than to the devocalized males. This was the case for both silent and vocalizing females. It appears, then, that devocalized males are inferior to vocalizing males with regard to the capacity to induce female paracopulatory behaviors. However, this has no consequence for sexual interaction, since silent and vocalizing male copulated equally. In sum, these data show that vocalizations play a very limited role in rat sociosexual behavior in a seminatural environment. Furthermore, this indicate that vocalizations have no evident function in partner selection (preference) during copulatory interactions.

5:00-6:00 ***New cellular insights into the maintenance of memory in mammals and mollusks.*** Chair: David Glanzman.

PKMzeta, LTP and Memory. Sacktor, Todd C.1 1Department of Physiology and Pharmacology, State University of New York Downstate Medical Center, Brooklyn, NY 11203 USA. Long-term memories are believed to be due to persistent changes in synaptic strength. Although the molecular mechanisms initiating these changes have been extensively studied, the mechanisms maintaining these changes, which may contribute to storing long-term memory, have been unknown. Recently, however, a candidate molecular mechanism has emerged for maintaining a persistent form of synaptic enhancement triggered by strong afferent stimulation of synapses, long-term potentiation (LTP). The key molecule in this maintenance mechanism is a brain-specific, protein kinase C isoform, PKMζ. Unlike other PKC isoforms that require second messengers for activation, PKMζ is constitutively and thus persistently active. Evidence suggests that the persistent activity of the kinase is both necessary and sufficient for maintaining synaptic enhancement in LTP. Likewise, PKMζ inhibition has been found to disrupt the storage of previously established long-term memories. Recently, however, the role of PKM was challenged by data obtained from PKM-knockout mice that nonetheless show normal appearing LTP and long-term memory. Moreover, like in wild-type mice, LTP and memory in PKM-null mice are disrupted by the inhibitor ZIP. Two hypotheses can account for these findings. First, PKMζ is unimportant for LTP or memory. Second, PKMζ is essential for late-LTP and long-term memory in wild-type mice, and PKMζ-null mice recruit compensatory mechanisms, which are also inhibited by ZIP. We found that whereas PKMζ persistently increases in LTP maintenance in wild-type mice, PKCι/λ, a closely related gene-product that, like PKM, is inhibited by ZIP, persistently increases in LTP maintenance in PKMζ-null mice. Using a pharmacogenetic approach, we found PKMζ-antisense in hippocampus blocks late-LTP and spatial long-term memory in wild-type mice, but not in PKMζ-null mice without the target mRNA. Conversely, a PKCι/λ-antagonist disrupts late-LTP and spatial memory in PKMζ-null mice, but not in wild-type mice. Thus, whereas PKMζ is essential for wild-type LTP and long-term memory, persistent PKCι/λ activation compensates for PKMζ loss in PKMζ-null mice. Persistently increased atypical PKC activity by either PKMζ or PKCι/λ is the common molecular mechanism for maintaining late-LTP and spatial long-

term memory in wild-type and PKMζ-null mice. T.C.S. is supported by NIH MERIT Award R37 MH057068, R01 MH53576, and R01 DA034970.

PKM stabilizing proteins in long-term memory. L. Ferguson1, S. Chen2, J. Park2, d. Glanzman2, W. Sossin1; 1Neurol. and Neurosurg., McGill Univ., Montreal, QC, Canada; 2Dept. of Integrative Biol. and Physiol., Univ. of California, Los Angeles, CA. In the Aplysia sensory-motor neuron synapse, there is a tight link between serotonin-induced forms of synaptic plasticity and memory for sensitization in the animal. The cleavage of PKCs by calpain to form persistently activated PKCs, called PKMS, is important for both intermediate stages of synaptic plasticity that are independent of gene expression and for longer-lasting stages of synaptic plasticity that do require gene expression. Moreover, distinct PKCs are cleaved into PKMs in distinct compartments (presynaptic vs postsynaptic) and by distinct stimulation paradigms. However, distinct PKMS expressed in the motor neuron are sufficient to increase synaptic strength. We are interested in the products of gene expression that interact with the calpain-mediated cleavage of PKCs into PKMs. One candidate for this process is the protein Kibra, whose mRNA is upregulated during learning and in vertebrates has been shown to stabilize PKM zeta through direct binding. We expressed Kibra and a Kibra mutated at the putative PKM binding site (KIbraΔPKC binding) in Aplysia neurons together with either a PKM generated from the classical PKC, PKC Apl I or a PKM generated from the atypical PKC III (an orthologue of PKC zeta). We found strong stabilization of PKM Apl III that depended on the known PKM binding site, but only weak stabilization of PKM Apl I that actually increased when the putative PKM binding site was mutated. Thus, Aplysia Kibra differentially stabilized PKM Apl III and PKM Apl I and appears to use distinct sites to stabilize the two different isoforms. The implication of this for the specificity of PKMs for memory formation will be discussed. Supported by Canadian Institute of Health Research grant to W.S.

Multiple calpains can mediate formation of protein kinase Ms involved in memory-related synaptic plasticity. Margaret H. Hastings1, Carole Abi Farah1, Tyler W. Dunn1, Jiangyuan Hu2, Diancai Cai3, Shanping Chen3, Katrina Gong1, Xiaotang Fan1, Joanna K. Bougie1, Danay Baker-Andresen1, Samuel Schacher2, David L. Glanzman3 and Wayne S. Sossin1. 1McGill University, 2Columbia University, 3University of California, Los Angeles. Pharmacological inhibitors of the cytosolic cysteine protease calpain disrupt induction of synaptic plasticity and memory in species ranging from rodents to bees and molluscs. In vitro, calpains can mediate limited proteolysis of a wide range of synaptic proteins, which has led to a nebulous array of mechanistic models for calpain's role in memory. One possible explanation for the diversity of functions attributed to calpain may be the number and diversity of the calpain family members themselves. The calpains comprise a large, ancient superfamily of proteases, and animals generally possess multiple isoforms. In the mollusc Aplysia, calpain is thought to contribute to memory through proteolysis of protein kinase C (PKC) to produce a constitutively active catalytic fragment known as protein kinase M (PKM), but the calpain isoform involved has not yet been determined. Using live imaging FRET-based cleavage assays and dominant negative calpains in a cell culture analog of behavioural sensitization, we found that an Aplysia classical calpain, but not SOL calpain, is required for cleavage of classical and atypical PKC during two distinct forms of intermediate-term synaptic facilitation. Classical calpain was also required for facilitation itself. However, the dominant negative SOL, but not the dominant negative classical calpain, decreased PKC cleavage in an overexpression-induced positive feedback loop modeling persistent PKM formation in long-term memory. Our results suggest that multiple calpains may contribute to PKM-dependent synaptic plasticity underlying different forms of memory.

The role of PKM and epigenetic mechanisms in the consolidation and maintenance of long-term memory. David L. Glanzman 1,2,3, Kaycey Pearce1, Diancai Cai1, Shanping Chen1, Adam C. Roberts1. 1Department of Integrative Biology and Physiology, UCLA, Los Angeles, CA, 2Department of Neurobiology, David Geffen School of Medicine at UCLA, Los Angeles, CA, 3Integrative Center for Learning and Memory, Brain Research Institute, UCLA, Los Angles, CA. The cellular mechanisms of long-term memory (LTM) consolidation and maintenance in the brain remain mysterious. Taking a reductionist approach, we have investigated the mechanisms underlying the consolidation and

maintenance of the LTM for behavioral sensitization in the marine snail Aplysia. Previously, we observed that PKM Apl III, the Aplysia homolog of mammalian PKMζ, played a critical role in the maintenance of LTM. Inhibition of PKM Apl III, through treatment with chelerythrine, an inhibitor of protein kinase C (PKC), or the pseudosubstrate-based peptide ZIP, disrupted even well consolidated LTM, as well as long-term facilitation (LTF), the synaptic basis of long-term sensitization. More recently, we reported that prior treatment with the histone deacetylase (HDAC) inhibitor trichostatin A (TSA) blocked the disruption of LTM maintenance by chelerythrine. This result implies that chelerythrine's disruptive effect on LTM was due, in part, to gene silencing through histone deacetylation. To further explore the role of epigenetic mechanisms in the consolidation of LTM in Aplysia, we tested whether DNA methylation plays a role. Accordingly, we injected the DNA methyltransferase (DNMT) inhibitor RG108 into animals immediately after sensitization training. When tested at 24 h after training animals that received the injection of RG108 did not exhibit LTM. Similarly, animals treated with anisomycin, a protein synthesis inhibitor, immediately after training did not exhibit LTM at 24 h. These results raise the possibility that inhibition of DNMT and of protein synthesis might have related effects on the consolidation of LTM. But modest additional sensitization training, which in naïve animals does not produce LTM, was able to reinstate LTM in animals given post-training anisomycin treatment; by contrast, we could not reinstate LTM in animals given post-training treatment with RG108. Interestingly, LTM also could not be reinstated following an injection of anisomycin prior to, rather than immediately after, long-term sensitization training. Taken together, our results imply that PKM Apl III and protein synthesis play roles in epigenetic actions that contribute significantly to memory consolidation. PKM Apl III appears to mediate histone acetylation of memory-related genes. Protein synthesis during, but not after, training may be important for regulating DNA methylation. For example, long-term sensitization training may trigger the synthesis of proteins that mediate the silencing, via DNA methylation, of one or more genes that act to repress memory; the silencing of the repressor gene(s) may be critical for the consolidation, and perhaps maintenance, of LTM. Funding sources: NINDS, NIMH, NSF

6:30-8:30 **Poster Session 2.**

1. **A novel oxytocin-like compound reduces motivation to self-administer methamphetamine and relapse to methamphetamine seeking in rats.** SarahBaracz1,2, NicholasEverett1, MichaelBowen2, MichaelKassiou2, JenniferCornish1, IainMcGregor2. 1Macquarie University, NSW, Australia 2 University of Sydney, NSW, Australia. The psychostimulant methamphetamine (METH) is an addictive illicit drug. The neuropeptide oxytocin has been shown to robustly reduce METH-related reward and abuse in rodents. However, its poor permeability of the blood brain barrier and limited oral bioavailability impacts on its therapeutic potential. The recent development of synthetic oxytocin-like compound -1 (SOC-1), a small molecule with enhanced blood brain barrier penetration and oral bioavailability with oxytocin-like effects on enhancing social behaviours, is a promising therapeutic alternative. The ability of SOC-1 to reduce METH abuse and relapse, although, had not yet been investigated. The aim of the study was to investigate whether SOC-1 administration reduces motivation for METH intake and drug-primed reinstatement to METH-seeking behaviour. Male Sprague Dawley rats with implanted jugular vein catheters were initially trained to self-administer METH (0.1 mg/kg/infusion) under a fixed ratio 1 schedule of reinforcement. Rats then advanced to a progressive ratio (PR) reinforcement schedule to examine the effect of SOC-1 (0, 1.25, 2.5, 5, and 10 mg/kg) intraperitoneal (ip) administration on motivation for METH taking, or underwent testing of SOC-1 (0, 2.5, 5, and 10 mg/kg; ip) effects on drug-primed reinstatement of METH seeking following extinction. Our results showed that SOC-1 administration reduced PR responding for METH (5mg/kg and 10mg/kg doses) and relapse to METH-seeking behaviour (all tested doses). Overall, these findings demonstrate that SOC-1 has similar effects to oxytocin on reducing methamphetamine-taking and -seeking behaviours and provides further support for its application as a therapeutic tool. This work was supported by an NHMRC grant 1088711.

2. **Effect of Bupleurum falcatum on behavioral sensitization and enhanced dopaminergic expression.** Dae-Hyuk Jang, Hyun-ju Lee, Dae-Hyun Hahm, Hye-Jung Lee and Insop Shim1. 1Acupuncture and Meridian Science Research Center, College of Korean Medicine, Kyung Hee University, Seoul, Republic

of Korea. Bupleurum falcatum (BF) is used in traditional oriental herbal medicine for the treatment of psychosomatic disorders and problems in digestive system. Its anti-inflammatory effect and liver function improving effect has been investigated but influence on nicotine addiction has not been examined yet. The present study was designed to assess the ability of the ethanol extract of Bupleurum falcatum (EBF) on nicotine-induced increased expression of c-fos and tyrosine hydroxylase(TH) and behavioral hyperactivity. Rats were pretreated with EBF 30 min before repeated injections of nicotine (0.4 mg/kg, subcutaneously, for 7 consecutive days). After 3 days withdrawal of nicotine, nicotine was re-treated on the 11th day. Locomotor activity was measured during 7-day nicotine treatments and 11th day. After behavioral test rats were sacrificed to assess expression of c-fos and TH in the nucleus accumbens (NA) and the ventral tegmental area (VTA) respectively. EBF inhibited development of nicotine-induced sensitization and increased expression of c-fos in the core and shell of NA. Also, EBF prevented enhanced expression of TH in the VTA induced by repeated nicotine treatment. Taken together, these results demonstrate that BF has the possibility of preventing nicotine addiction by attenuating behavioral sensitization and enhanced dopaminergic expression.

3. **Potential role of wolfberry extract in the drug abuse rehabilitation: Protective effect of Lycium barbarum polysaccharide on dextromethorphan-induced neurogenesis and mood impaired rats.** Po, Kevin Kai-ting1; Siu, Andrew Man-hong1; Chan Jackie Ngai-man1; So, Kwok-fai2; Fung Kai-hang1; Lau, Benson Wui-man1. 1. The Hong Kong Polytechnic Universit. 2. The Hong Kong University. Cough syrup abuse is a very common worldwide problem which can cause neurological disease, while effective and direct treatment for the abusers is still lacked. The main component of cough syrup, dextromethorphan (DXM), causes affective symptoms such as severe anxiety and depression in human if consumed chronically. An earlier animal study conducted by our team has shown that impairment of neurogenesis exists in the rats with repeated DXM administration. Lycium barbarum Polysaccharides (LBP), a traditional Chinese herbal medicine, was shown to have the ability to protect animal from the induction of depressive behavior in different disease models with impaired neurogenesis. However, there is little empirical research that provides further evidences concerning the protective effect of LBP on DXM abuse. In this study, we investigated the protective effect of LBP, on behavioral and neurological deterioration due to cough syrup abuse. In the current animal study, the potential therapeutic effect of LBP in DXM-treated rat was studied by behavioral and histological methods. After a treatment period for 2 weeks, the animals were subjected to behavior testes for anxiety and depression-like behavior, including forced swimming test and open field test. After behavior testes, the rats were sacrificed and their brain tissues were prepared for histological analysis related to neurogenesis. The behavior testes revealed that LBP can reduce the depression-like behavior in rats with DXM treatment but have no beneficial effect in the normal control with water as vehicle. In the same line, histology results have also shown that LBP can alleviate the hindrance of neurogenesis in hippocampus in rats induced by DXM treatment but not in the normal control. The findings have indicated that LBP can benefit DXM-treated rats in terms of behavior and neurogenesis. General health of the DXM treated rats were also improved by LBP by using body weight as indicator. The results are consistent with previous studies and provide insights for using wolfberryas a more focusing treatment for cough syrup abusers. Funding source: Departmental General Research Fund (RS, HK PolyU): GUB47.

4. **Determining Mechanisms behind the Blunted Response to Stimulants in Toxoplasma gondii Chronically Infected Mice.** Ross McFarland1, Zi Teng Weng2, David Sibley2, Jay Baraban3, Robert Yolken3,4, Mikhail Pletnikov1,3. 1 Johns Hopkins Bloomberg School of Public Health, 2 Washington University in St. Louis, 3 Johns Hopkins University School of Medicine, 4 Stanley Medical Research Institute. Infection with the neurotropic parasite Toxoplasma gondii has been known to be a risk factor for the development of schizophrenia in humans, and to impact rodent performance on several behavioral assays. In work previously presented, our lab has shown that chronic infection in mice massively reduces the animals' response to amphetamine in open field activity. Additionally, work completed more recently has shown that the reaction to cocaine is also severely blunted in infected animals. Both drugs impact the release of dopamine within the reward circuitry of the brain, suggesting that infection with the parasite is

interfering with dopamine release or reuptake. The relationship to dopamine is critically important in translating animal behavioral data and generating relevance for human psychiatric health. We have two potential mechanistic pathways currently under experimentation, detailed here. The first utilizes Toxoplasma strains that have had an endogenous tyrosine hydroxylase gene knocked out using CRISPR/Cas-9. The depletion of this genetic element, which has been implicated in directly impacting dopamine levels in the infected animal brain, will allow us to determine the possible role of the parasite in directly impacting dopamine transmission. The second mechanistic possibility is that microglial activation is driving decreased release of dopamine from neurons of the substantia nigra and ventral tegmental area. We have also detailed how we are approaching this possibility using microdialysis and targeted interference with microglial polarization.

5. **The role of mGluR5 in neurobiological mechanisms of resilience to develop comorbid PTSD and cocaine addiction.** Marek Schwendt1 and Lori Knackstedt1. 1 University of Florida, Gainesville, FL, USA. Exposure to traumatic life events leads to the development of post-traumatic stress disorder (PTSD) in a subpopulation of trauma-exposed individuals. In addition, 50-65% of PTSD patients also have substance use disorder (SUD), a rate that is three to five times higher than in the non-PTSD population. We have developed an animal model of PTSD-cocaine comorbidity that studies cocaine-taking and cocaine-seeking in separate subpopulations of animals that show vulnerability or resilience to develop PTSD-like symptoms. First, Sprague-Dawley rats underwent a single exposure to predator-associated stimulus (TMT,a fox pheromone). One week later, approximately 20% of rats (termed “PTSD-like” or vulnerable rats) displayed increased anxiety in elevated plus maze and sensitization of the acoustic startle response; approximately 20% were termed “Resilient”, with no manifestation of anxiety; and the remainder showed signs of anxiety in only one measure and were eliminated from the experiment. In order to characterize changes in brain circuitry and identify neurobiological markers of PTSD resilience vs. susceptibility, expression of glutamatergic and glucocorticoid markers were evaluated in anxiety-related brain regions. We found that increased expression of mGluR5 in the prefrontal cortex and amygdala is associated with resilience to PTSD. Stress-related genes such as CRH and Glcci1 were elevated in multiple brain areas by TMT exposure, but did not show different patterns of expression in Resilient or PTSD rats. PTSD rats did not differ from their resilient counterparts in the rate of cocaine self-administration, but displayed reduced extinction and enhanced cocaine-seeking during a cue-prime reinstatement test. The beta-lactam antibiotic was unable to attenuate reinstatement only in PTSD rats, but prevented reinstatement in Resilient and control rats. Repeated daily administration of mGluR5 positive allosteric modulator CDPPB (30mg/kg i.p.) enhanced operant extinction learning as well as fear extinction and in combination with ceftriaxone, blocked cue-primed reinstatement of cocaine-seeking. Taken together, these results suggest that upregulation of mGluR5 function in the brain can promote resilience to PTSD-like anxiety as well as reduce relapse to cocaine-seeking.This mechanism might be utilized in development of novel neurobiologically-based PTSD therapies. Supported by: DOD award no. W81XWH-12-2-0048.

6. **Mapping of the prenatal and adult methamphetamine effects on D1-like dopamine, M1 and M2 muscarinic receptors in rat central nervous system.** Slamberova, Romana1; Farar, Vladimir2; Valuskova, Paulina3; Myslivecek, Jaromir3. 1Charles University in Prague, Third Faculty of medicine, Department of Normal, Pathological and Clinical Physiology, Prague, Czech Republic. 2Institute of Medical Biochemistry and Laboratory Diagnostics, First Faculty of Medicine, Charles University, 12800 Prague, Czech Republic. 3Institute of Physiology, First Faculty of Medicine, Charles University, 12800 Prague, Czech Republic. Dopaminergic receptors are implicated in many neurological processes, including motivation, pleasure, learning and memory, and fine motor control. Muscarinic receptors (MR) for acetylcholine are widely distributed in the CNS and are considered as important factors in some psychiatry disorders. Methamphetamine (MA) is worldwide known drug with high potential for addiction that causes dopamine, noradrenaline and serotonin release in the central nervous system (CNS). Studies show that MA is also able to increase acetylcholine levels in adult rodents. The aim of the present study was to map changes in D1-like dopamine receptors (DR), M1 and M2 muscarinic receptors (MR), and the

total number of MR (i.e. M1-M5 MR) in the CNS of rats exposed to MA prenatally and in adulthood. Rat mothers were exposed to MA (5 mg/kg s.c.) or saline (1 ml/kg s.c.) during the entire gestation period. Their male offspring were then tested in adulthood. 12 prenatally MA-exposed and 12 prenatally saline-exposed male rats were administered in adulthood with single MA (1 mg/kg) or single saline injection. Thus, based on prenatal drug exposure and the acute adult treatment, the animals were divided to 4 experimental groups: Prenatally MA-exposed rats treated with saline (MA/S) or MA (MA/MA) in adulthood and prenatally saline-exposed rats treated with saline (S/S) or MA (S/MA) in adulthood. One hour after the acute treatment animals were sacrificed and their brains were removed, frozen in dry ice and stored at -80 ˚C until cryosectioning. Sagital brain sections of 16 □m thickness were cut on a cryostat at -20˚C, thaw-mounted on Superfrost Plus glass slides and kept in storage boxes at -80°C until use. The numbers of M1, M2 total MR, and D1-DR were measured by autoradiography. The main effect was detected in the hippocampus. The most affected receptors were M1 MR. D1-DR were decreased in motor cortex and substantia nigra. M1MR were decreased in caudate-putamen, dorsal hippocampus, CA1, CA3 and dentate gyrus (DG). M2MR were decreased in DG only. Total number of MR was moreover decreased in dorsal hippocampus, CA1, CA3 and DG. Our results have shown different patterns of changes in DR and MR, suggesting a pilot role of M1 MR in the CNS changes induced by combined prenatal and adult MA exposure. Our findings bring new light into the research of drug addiction and help to explain the mechanisms of some psychiatry disorders. Supported by: GACR 14-03708S, PRVOUK P34.

7. **Altered long-term platicity of glutamatergic synapses in the nucleus accumbens of alcohol-dependent rats.** Giuseppe Talani1, Gabriele Sarigu2, Laura Firino2, Francescangelo Vedele2, Luca Picci2, Giovanni Biggio1,2, Enrico Sanna1,2. 1Institute of Neuroscience, National Research Council (CNR), Cittadella Universitaria, Monserrato, Italy. 2Dept of Life and Environmental Sciences, Sect of Neuroscience and Anthropology, University of Cagliari and C.N.R. Institute of Neuroscience, Cagliari Italy. Dependence from substances of abuse such as alcohol (EtOH), impairs several cognitive and executive functions, making EtOH addiction one of the major public health problem in the western world. At central level, EtOH addiction may cause activity-dependent structural remodeling that is thought to confer addictive-like behaviors, such as excessive ethanol drinking and relapse. EtOH has a widespread site of action in the central nervous system but the nucleus accumbens (NAcc) seems one of the most important areas involved in neuronal adaptations. NAcc plays a central role in neural circuits responsible for goal-directed behaviors during addictive states. Its activity is heavily modulated by glutamate (GLU)- and dopamine (DA)-containing projections that originate in cortical and limbic regions and converge on a common postsynaptic target: the medium spiny neuron (MSN). As recently reported, impairments on dendritic spines shape and number, are related to synaptic dysfunctions occurring upon ceasing the use of chronic EtOH consumption. Changes in spine morphology, such as selective pruning of long-thin spines, were also accompanied by a marked reduction in NMDA-dependent Long-Term Depression (LTD). All these modifications seem related to a “hypodopaminergic state” that, in turn, might be the underlying cause of selective spine culling which, by depriving GLU transmission from its post-synaptic element, strongly decrease the expression of LTD. To better elucidate about the role of DA on neuronal modification during EtOH withdrawal (EtOH-Wdl) we test whether L-DOPA treatment reverses the loss of dendritic spines in MSNs of the Nacc shell and LTD formation. Patch-clamp experiments from Nacc slices obtained from EtOH-Wdl revealed that 5 min slice perfusion of DA (10 microM) restored the level of LTD to the values observed in both controls and EtOH chronic treated animals. A single injection of L-DOPA (6 mg/kg) one hour before sacrifice was able to restore the LTD levels in EtOH-Wdl animals compared to controls. Furthermore we also focused our experiment in measuring the NMDA/AMPA ratio that, as reported previously, resulted diminished during withdrawal syndrome and treatment with dopamine in slice or L-DOPA systemic injection are also able to restore this parameter to values similar to those observed in controls. Interestingly, the D1 receptor antagonist SCH23390 but not the D2 antagonist sulpiride, was able to antagonize the effect of DA perfusion on reversing the withdrawal-induced changes suggesting that the D2 containing MSNs are less involved in the effect of withdrawal in alcohol dependent rats. Overall our findings suggest that DA reflect a key role in withdrawal symptoms in alcohol dependent

rats; our results will permit to pave the way for newer therapeutic possibilities in alcoholism by boosting a defective dopamine transmission.

8. **Alcohol induced locomotor activity is mediated by dopamine D2-like receptors in zebrafish.** Steven Tran1, Amanda Facciol2, Magda Nowicki2, Diptendu Chatterjee2, Robert Gerlai1, 2. 1Department of Cell & Systems Biology, and 2Psychology, University of Toronto. Alcohol addiction is a debilitating disease costing hundreds of billions of dollars annually due to lost productivity and required healthcare. Sensitivity to alcohol's stimulant effect has been identified as a risk factor for the development of alcohol addiction, yet the mechanism of this effect is poorly understood. Using zebrafish, we investigated a potential dopaminergic mechanism underlying alcohol's stimulant effect. In the current study we first demonstrate that acute exposure to 1% alcohol for 60 minutes increases locomotor activity (i.e. total distance moved) as well as whole-brain tissue levels of dopamine quantified by high precision liquid chromatography (HPLC). To investigate the mechanism of the alcohol induced increase of dopamine, we examined tyrosine hydroxylase, the rate-limiting enzyme responsible for dopamine synthesis. Enzymatic activity assays revealed that acute exposure to 1% alcohol increased the activity of tyrosine hydroxylase as measured from whole-brain tissue in vivo as well as ex vivo, in a time- and concentration-dependent manner. Western blot analysis of whole-brain tissue revealed that acute exposure to 1% alcohol also increased the expression of tyrosine hydroxylase. We further examined the change in spatial expression of this protein in the zebrafish brain following exposure to 1% alcohol. Our preliminary analysis revealed that acute alcohol exposure increased tyrosine hydroxylase protein expression in the zebrafish brain in a region-dependent manner. To further explore the mechanistic link between alcohol induced locomotor activity and dopamine, we examined the potential role of different dopamine receptors using a psychopharmacological approach. We found that pre-treating zebrafish with haloperidol (a dopamine D2-like receptor antagonist) attenuated alcohol induced locomotor activity. To identify specific neuronal populations of dopamine D2 receptors in the zebrafish brain activated by alcohol exposure, we examined c-fos protein expression as a method of determining neuronal activation. Western blot analysis revealed that 1% alcohol induced peak c-fos expression at 90 minutes post-exposure. We are currently examining the co-localization of dopamine D2 receptors and c-fos expression in the zebrafish brain following 1% alcohol exposure. Our results identified dopamine as an important regulator of alcohol induced locomotor activity in zebrafish. In summary, our findings show that acute exposure to alcohol increases whole-brain dopamine via induction of tyrosine hydroxylase leading to activation of dopamine D2-like receptors. Funding: Research was funded by an NSERC Discovery Grant issued to Robert Gerlai, and an NSERC CGSD issued to Steven Tran.

9. **The role of copa and CB1 receptor in cocaine-induced locomotor sensitization and JWH-210-induced dopamine release.** Jaesuk Yun, Tac-hyung Lee, Young-Hoon Kim, HyeJin Cha , Hye-Kyung Park and Hyung Soo Kim. National Institute of Drug and Safety Evaluation, Ministry of Food and Drug Safety, Osong, Cheongju, Republic of Korea. Acorrding to FDA guideline on abuse potential evaluation, clinical test should be performed with patients who have experiences of drug abuse. To exclude a possibility of false negative results in drug abuse potential evaluation, government authority needs to consider more sensitized animal model to test new psychoactive substance dependence. In present study, we are aim to clarify the molecular target underlying abused drug-induced dependence or biochemial abnormality in abuse-related brain regions. Cocaine was treated for 5 days to induce locomotor sensitization in SD rats, and nucleus accumbens was sampled for further DNA microarray study. We demonstrated that pre-treatment of cocaine (15 mg/kg) induced locomotor sensitization induced by cocaine challenge in comparison with saline pre-treated rat. In addition, DNA microarray revealed that the expression levels of 40 genes was changed in cocaine-induced sensitized rats' nucleus accumbens. JWH-210 administration induced conditioned place preferences in ICR mice and increment of dopamine release in nucleus accumbens. We also showed that the expression levels of 8 genes were significantly changed by JWH-210 treatment. Furthermore, we demonstrated that copa and CB1 receptor mRNA expression was upregulated and downregulated by JWH-210 administration, repectively. Therefore, we sought to examine a role of copa and CB1 receptor in JWH-210 induced dopamine

release. We will present the effect of CB1 knock-down on dopamine release in PC12 cells. This study was supported by 16181MFDS413 and 15181MFDS482.

10. **Ceftriaxone and cocaine relapse: Contrasting the roles of xCT and GLT-1 upregulation.** Lori A. Knackstedt1. 1 University of Florida, Gainesville, FL, USA. Ceftriaxone is a beta-lactam antibiotic which increases the expression and function of the glutamate transporter GLT-1 and of system xC- (Sxc), which exchanges extracellular cysteine for intracellular glutamate. Basal glutamate levels in the NA (NA) are largely controlled by Sxc and a decrease in its activity is a contributing cause of the altered glutamate homeostasis observed in this brain region following cocaine self-administration in rats. The catalytic subunit of Sxc is xCT, and we have demonstrated that expression of xCT and GLT-1 is decreased in the NA core following cocaine self-administration. We have also shown that ceftriaxone attenuates cue- and cocaine-primed reinstatement while restoring levels of both xCT and GLT-1 in the NA core. At this time it is not known if alterations in both transport systems mediate the altered synaptic plasticity in the NA after cocaine self-administration. Here we used a morpholino antisense strategy to decrease the expression of xCT protein and examined basal levels of glutamate and GluA1 and GluA2 expression. We found that xCT antisense infusion into the NA core significantly decreased basal glutamate. We also found an increase in NA GluA1 expression in cocaine self-administering rats and no change in GluA2 expression. In rats that had self-administered cocaine and received intra-NAc infusion of xCT antisense, this increase in GluA1 was potentiated. In a separate group of rats, we utilized a viral vector to selectively upregulate glial GLT-1 expression in the NA core and found no impact on the reinstatement of cocaine-seeking. GLT-1 upregulation via AAV did not produce an accompanying increase in xCT expression. These data support the importance of xCT expression in maintaining basal glutamate in the nucleus accumbens and point to basal glutamate levels as a key mediator of post-synaptic AMPA receptor alterations. Furthermore, the upregulation of GLT-1 alone is not sufficient to suppress cocaine-seeking. Taken together, these results indicate that medications targeting GLT-1 upregulation alone will not be sufficient to reduce cocaine relapse.

11. **Examining the effect of chronic intranasal oxytocin administration on the neuroanatomy and behaviour in two different autism-related mouse models.** Buchwald, Zsuzsa[1]; Stuive, Monique[1]; Ellegood, Jacob[1]; Anagnostou, Evdokia[2]; Lerch, Jason[1]. [1]Mouse Imaging Center, Hospital for Sick Children, Toronto, Canada, [2]Holland Bloorview Kids Rehabilitation Center. Introduction: Autism is a neurodevelopmental disorder characterized by social communication deficits and repetitive behaviors. Oxytocin is known for its ability to promote social behaviours and may be a promising therapeutic for autism. To determine what might contribute to response susceptibility, we treated the 16p11.2 deficiency and FMR1 knockout mouse models with intranasal oxytocin. Methods: Intranasal oxytocin was administered once a day, for 28 days, starting at 5 weeks of age. During the third week of treatment, the behaviour of the mice was assessed in multiple domains, including sociability and repetitive behaviours. The mice underwent in vivo and ex vivo neuroimaging throughout various points in the study. Results: Treatment had no significant effect on neuroanatomy and, for the most part, did not enhance the behaviours of either mouse model, though it slightly increased social behaviours in the 16p11.2 mouse. Discussion: Neither model showed a treatment effect in their neuroanatomy, and very little effect on behaviour. This indicates that oxytocin may not be a good treatment option for either the 16p11.2 or FMR1 mutant mice, and therefore humans with the 16p11.2 mutation and children with Fragile X Syndrome. Future directions involve looking at the response of multiple strains of autism-related mouse models to several promising therapeutics used in human patients with autism, yielding the ability to establish a translational paradigm for predicting responders from non-

12. **Mild Behavioural Impairments in Shank3 Mutant Mice, a mouse model for autism spectrum disorders.** Allain-Thibeault Ferhat1,2,3, Anne-Marie Le Sourd1,2,3, Thomas Bourgeron1,2,3, Elodie Ey1,2,3. 1 Human Genetics and Cognitive Functions, Institut Pasteur, Paris, France. 2 CNRS UMR 3571 'Genes, synapses and cognition', Institut Pasteur, Paris, France. 3 University Paris Diderot, Sorbonne Paris Cité, Human Genetics and Cognitive Functions, Paris, France. Autism Spectrum disorders (ASD)

are psychological neurodevelopmental disorders affecting more than one person over 100 people. Diagnosis is based on two main criteria: alteration of social communication and interaction as well as repetitive and stereotyped behaviours (DSM-5). ASD have a strong genetic component and over 200 genes are associated with ASD. An important part of these genes, such as NEUROLIGIN1-4, NEUREXIN1-2, or SHANK1-3, encodes for proteins expressed in excitatory or inhibitory synapses. Around 1% of patients with ASD carry a mutation in one of the three SHANK genes: SHANK1: 0.07%, PROSAP1/SHANK2: 0.17%, PROSAP2/SHANK3: 0.73% . SHANKs are scaffolding proteins composed of several interaction domains and located in postsynaptic density (PSD) of glutamatergic synapses. Here we characterise the Shank3 mouse model carrying a mutation in exon 11, involved in the SH3 domain (Src homology 3 domain). The present study aims at proposing a longitudinal study of a mouse model for autism spectrum disorders to shed light on the stability of the phenotype. We focus on social behaviour, stereotyped behaviours and locomotion measured at three different time points: 3, 8 and 12 months of age. We evaluate the evolution of the phenotype and observable comorbidities. We test Shank3-KO, Shank3-HZ and Shank3-WT male and female littermates. At three months of age, the Shank3-KO mice display an important increase in stereotyped behaviours, more specifically self-grooming, mild impairments in social interactions, as well as an important reduction of the locomotion in comparison with wild-type littermates. Between 3 and 12 months of age, a worsening of the phenotype can be observed for several features, especially self-grooming. This characterisation will be complemented by electrophysiological investigations in the cerebellum and in the prefrontal cortex. These data suggest that the ProSAP2/Shank3 knock-out mouse will be relevant for further pharmacological treatments.

13. **Heterozygous deletion of GTF2i results in hypersocial behavior, but duplication of this gene has no effects on social behavior in mice: implications for Williams Beuren Syndrome and Autism Spectrum Disorder.** Loren Martin1, Erica Iceberg1, Gabriel Allaf1, Cassandra Liew1, Maryann Slama1 and Julie Engelmann1. 1Azusa Pacific University. Williams Beuren Syndrome (WBS) is a disorder caused by a deletion at human chromosome 7q11.23, with symptoms including mild to moderate intellectual disability and hypersocial behavior. Autism Spectrum Disorder (ASD) is a behaviorally-defined collection of syndromes of known and unknown etiology that share a common phenotype including impairments of social motivation. The hypersocial behavior associated with WBS appears opposite to the hyposocial behavior observed in ASD and, interestingly, duplications of 7q11.23 have been associated with ASD. The social phenotype of WBS has recently been linked to deletion of a single gene: GTF2i, or general transcription factor IIi (TFII-I). Duplication of GTF2i has also recently been associated with ASD, suggesting that it works in a dosage-type response in its effects on social behavior. In this study, we characterized the specific aspects of social behavior that are modulated by GTF2i by comparing mice having either a deletion (GTF2i+/-) or duplication (GTF2i+/Dup) of GTF2i to wildtype (WT) littermate controls in a series of social behavior tasks. Results from tests comparing GTF2i+/- mice to WT sibling controls have been completed but tests on GTF2i+/Dup mice are ongoing. In the social choice task, GTF2i+/- mice showed a significant preference for a stimulus mouse that was not observed in WT siblings. GTF2i+/- mice spent significantly more time in nose-to-nose contact compared to controls during social encounters and also demonstrated a significantly heightened preference for urine over water scents. To assess social motivation, test mice were trained to press a lever for a social reward in the form of 15s access to an unfamiliar stimulus mouse. The number of lever presses achieved in the final trial of a testing session was used as an index of social motivation (breakpoint). GTF2i+/- mice demonstrated significantly higher breakpoints than controls. The mice were then tested in an operant task involving a choice between food and social rewards. The percentage of total lever presses that were made for a social reward was significantly higher for the GTF2i+/- mice. Overall, GTF2i+/- mice consistently demonstrated increased social behavior across multiple testing paradigms supporting a role for this gene in the hypersocial phenotype of WBS. However, preliminary tests of GTF2i duplication mice do not support a role for this gene in the hyposocial phenotype of ASD.

14. **Developmental social isolation alters expression of neural proteins in adult zebrafish.** Soaleha Shams1, Diptendu Chatterjee2, Robert Gerlai1,2; 1Cell & Systems Biology Dept., Univ. of Toronto

Mississauga, Mississauga, ON, Canada; 2Psychology Dept., Univ. of Toronto Mississauga, Mississauga, ON, Canada. Given the existing knowledge on its genetics and development, the zebrafish serves as an excellent translational model for studying vertebrate physiology. More recently, zebrafish has been popular in behavioral neuroscience as it is a highly social species with a wide range of quantifiable behaviors. Similar to social mammals, the early social environment of zebrafish can significantly affect their subsequent expression of behaviors and functionality of neural systems. However, the effects of social deprivation in zebrafish beyond the larval stage remain relatively unknown. To investigate this, we generated socially-deprived zebrafish and compared them to socially-reared control fish in adulthood. We exposed groups of socially-deprived and control fish to live social stimulus fish for increasing amount of time (30 min, 2hrs, 24 hrs) and recorded their behavior. The coordinates for each fish were used to calculate behavioral variables such as locomotor activity, anxiety-like behaviors, and response to social stimulus. We also compared various brain nuclei in socially deprived and control zebrafish and quantified distributions of brain proteins involved in normal brain development and activation. We measured expression of Neu-N (a neuronal marker), synaptophysin (synapse protein), N-CAM (cell-adhesion molecule), GAP-43 (axon elongation protein), BDNF (brain derived neurotrophic factor) and c-fos (neuronal activation marker) in social and isolated fish. Here we report that early social deprivation can alter anxiety-like behavior and response to social stimuli in adult zebrafish. Furthermore, compared to control fish, in socially-deprived zebrafish we observed significant changes in neural proteins involved in attention, activity, and social behavior. Our findings provide further support towards establishment of zebrafish as a suitable animal model to study the behavioral and neural consequences of developmental social deprivation. Acknowledgements: Supported by NSERC.

15. **Deficiency of neurogranin, a susceptible gene for schizophrenia, causes behavioral phenotypes related to schizophrenia and immaturity of the dentate gyrus in mice.** Satoko Hattori1, Hideo Hagihara1, Yoshihiro Takamiya1, Toshiki Kameyama2, Yuya Ouchi13, Hidehito Inagaki14, Hiroki Kurahashi13,4, Freesia L Huang25, Kuo-Ping Huang25, Tsuyoshi Miyakawa1.,6. 1Division of Systems Medical Science, Institute for Comprehensive Medical Science, Fujita Health University, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan, 2Division of Gene Expression Mechanism, Institute for Comprehensive Medical Science, Fujita Health University, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan. 3Genome And Transcriptome Analysis Center, Fujita Health University, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan. 4Division of Molecular Genetics, Institute for Comprehensive Medical Science, Fujita Health University, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan. 25Program of Developmental Neurobiology, NICHD, NIH, Bethesda, MD. 6Section of Behavior Patterns, Center for Genetic Analysis of Behavior, National Institute for Physiological Sciences, Myodaiji-cho, Okazaki, Aichi 444-8787, Japan. Large-scale genome-wide association studies have identified susceptibility loci for schizophrenia in the gene encoding neurogranin (NRGN). Neurogranin is a neuron-specific calmodulin binding protein abundantly expressed in brain regions implicated in schizophrenia pathophysiology, such as the hippocampus and cortex. In previous studies, it was reported that neurogranin is involved in synaptic plasticity and long-term potentiation and that Nrgn knockout (KO) mice exhibit aberrant behavioral phenotypes involving deficits in cognitive functions and abnormal emotional behaviors. In this study, we examined additional behavioral abnormalities relevant to schizophrenia and molecular alterations in the hippocampal dentate gyrus (DG) of Nrgn KO mice. We subjected adult (>20 weeks old) Nrgn KO mice to a comprehensive battery of behavioral tests. The mutant mice exhibited a series of behavioral abnormalities that resemble those of schizophrenics, including hyper-locomotor activity and impairments in working memory, social behavior and sensorimotor gating. In the DG, mRNA expressions of immature and mature granule cell (GC) markers were not changed in almost allany young mutant mice (<10 weeks old). However, older animals (>20 weeks old) showed increased expression of immature GC markers and decreased expression of mature GC markers. Bioinformatics analyses of transcriptome data also revealed that the gene expression patterns of the DG of older mutants are significantly similar to those of normal young mice. These results indicated that Nrgn KO mice show ‘immimmature DG’ phenotype, which has been proposed as a novel endophenotype of schizophrenia, and that both genetic and undetermined (e.g., stress and aging) factors might act together to reverse matured GCs to a pseudo-immature status. Nrgn

KO mice might be a novel animal model recapitulating the fact that typical onset of schizophrenia occurs during late adolescence or early adulthood. The late onset of the immature phenotypes would provide unique opportunity for studying molecular mechanisms of the disorder. Funding: CREST, JST & KAKENHI, MEXT.r.

16. **Aberrant Cognitive Phenotypes and Altered Hippocampal BDNF Expression Related to Epigenetic Modifications in the Shank1 Knockout Mouse Model for Autism.** A. Özge Sungur1, Magdalena C.E. Jochner1, Hani Harb2, Ayşe Kılıç2, Holger Garn2, Rainer K.W. Schwarting1, Markus Wöhr1. 1 Behavioral Neuroscience, Experimental and Physiological Psychology, Philipps-University of Marburg, 35032 Marburg, Germany. 2 Institute of Laboratory Medicine and Pathobiochemistry and Molecular Diagnostics, Philipps-University of Marburg, Marburg, Germany. Autism spectrum disorders (ASD) are a class of neurodevelopmental disorders characterized by persistent social communication deficits across multiple contexts, together with repetitive patterns of behavior. Among the most promising ASD candidate genes is the SHANK gene family, including SHANK1. To study the contribution of SHANK1 mutations to ASD symptoms throughout development, Shank1+/+, Shank1+/-, and Shank1-/- mice were compared in behavioral assays developed to detect social communication and cognitive deficits as juveniles and adults. As juveniles, social approach and recognition were evident irrespective of genotype. In contrast, object recognition was affected by Shank1 deletion, with Shank1-/- mice being severely impaired, i.e. not showing a preference for the novel object. Furthermore, a significant increase in acetylation of histone H3 at the BDNF promoter was detected in the hippocampi of Shank1-/- juveniles. These epigenetic modifications were paralleled by increased BDNF expression levels in the hippocampi of juvenile Shank1-/- mice. In adulthood, Shank1-/- males and controls displayed normal social approach, but impaired social recognition. Object recognition was additionally impaired in adult Shank1-/- males. Conversely, adult Shank1-/- females exhibited deficits in social recognition only. In summary, the present findings indicate that Shank1 deletions lead to an aberrant cognitive phenotype and an increase in BDNF expression in the hippocampus possibly due to epigenetic modifications, together with age- and sex-dependent effects on social behavior. Support: Deutsche Forschungsgemeinschaft (DFG – WO 1732/1-1).

17. **A precision medicine genetic marker for core cognitive deficits in schizophrenia.** Diego Scheggia1, Maddalena Mereu2, Marco Armando3, Maria A. De Luca4, Genny Orso5 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. 3Department of Neuroscience, Bambino Gesù Children's Hospital, Piazza Sant'Onofrio 4, 00100 Rome, Italy. 4Department of Biomedical Sciences, Università di Cagliari, Italy. 5IRCCS E. Medea Scientific Institute, Conegliano, Italy. Antipsychotics are the first-line, chronic, most largely-used and costly medications for the management of schizophrenia. These drugs show massive individual variability and non-optimal efficacy, especially for schizophrenia-relevant cognitive deficits. Notably, there is no biological rationale that can predict a person's response to these treatments. Using combined and strictly translational studies in mice and humans, here we found that variations in the DTNBP1 gene, associated with reduced levels of dysbindin-1, confer better responses to antipsychotic treatments for schizophrenia core dysfunctions in executive control. Using multilevel ex vivo and in vivo approaches in genetically modified mice and drosophilae, we then established that the dysbindin-antipsychotics interaction resides in a unique potentiation of cortical dopamine/D2 signaling through the amelioration of astrocytic and presynaptic intracellular trafficking. These findings demonstrate a biological indicator for the implementation of personalized healthcare for cognitive disabilities in schizophrenia, pioneering the concrete use of pharmacogenetics to combat psychiatric disorders.

18. **Stimulation of the nucleus pontis oralis elicits low frequency oscillations at different frequencies in the prefrontal cortex and hippocampus in urethane anesthetized rats.** Bernat Kocsis, Harvard Medical School. Task dependent theta frequency coupling between prefrontal cortex (PFC) and hippocampus (HC) was demonstrated in different behavioral paradigms; in rodents the focus was on HC driving of theta oscillations in the PFC and theta synchronization of PFC neurons. There are however

major differences between the oscillatory dynamics in the two networks. First, on-going HC theta rhythm during exploration is usually associated with shorter intermittent theta segments in the PFC. Second, PFC is frequently generating characteristic oscillations of its own at ~2 Hz or 4 Hz which may co-occur or alternate with HC theta rhythm. It should be noted that these 2 Hz and 4 Hz rhythms seen in the rat during active waking behaviors are completely different from the wide-band delta activity characteristic for quiet waking and slow wave sleep both in PFC and HC. Theta generators have been extensively studied over the past half century. Investigations of the intrinsic 2-4 Hz oscillation in the PFC are limited however by the short and rare occurrence of these episodes. The present study introduces an experimental paradigm to overcome this obstacle. Local field potentials (LFP) were simultaneously recorded in the HC and PFC of rats under urethane anesthesia during short episodes of electrical stimulation (0.1 ms square waves at 100Hz, 10 s duraction) of the nucleus reticularis pontis oralis (RPO). Stimulation intensity was systematically varied, spanning a range from threshold to maximum, identified as intensities where low-frequency theta rhythm appears in the HC and where its frequency no longer increases. The LFP segments were extracted and subjected to FFT to obtain power density spectra. Peak frequencies were identified in the HC and PFC respectively, and the power at these two frequencies was calculated for both signals. We found that stimulation of the RPO which, as shown in numerous prior studies, generated theta (4-9 Hz) oscillations in the HC, also elicited a different LFP rhythm in the PFC between 2 and 4 Hz. Both rhythms were often present in the spontaneous LFPs, as well. The frequency of both rhythms showed linear relationships with RPO stimulus intensity. Peak powers also changed in a stimulus-dependent manner but the changes followed opposite trends, i.e. theta increasing, 2-4 Hz decreasing with higher RPO stimulations, suggesting a possible negative coupling between the two rhythms.

19. **CRHR1 Mediation of neuroplasticity and neuroinflammation in the hippocampus following global cerebral ischemia.** Patricia Barra de la Tremblaye1, PhD and Hélène Plamondon1, PhD. 1 Behavioural Neuroscience Group, Department of Psychology, University of Ottawa. Ischemic brain injury triggers restorative processes characterized by rapid neuronal growth and neuroplasticity, critical to optimize functional recovery of individuals post stroke. Brain-derived neurotrophic factor (BDNF) may be a promising avenue in the treatment of cerebral ischemic injury because this neurotrophin can enhance structural plasticity and cognitive performance. Mechanisms controlling release of BDNF are mediated by corticotrophin-releasing hormone (CRH) acting through its CRH type1 receptor in stressful conditions. However, whether CRH can mediate the release of BDNF in the reparative process triggered by ischemic injury remains to be characterized. Recently, we demonstrated that Antalarmin (ANT), a selective CRHR1 antagonist, can block the persistent neuroendocrine dysfunctions observed following global cerebral ischemia. In the study to be presented, we investigated the effect of ANT on the levels of BDNF and other plasticity markers, as well as on functional recovery after cerebral ischemia. Specifically, Male Wistar rats (N = 50) were subjected to sham surgery or global cerebral ischemia using the four vessel occlusion (4VO) model. ICV injection of ANT (2µg/2µl) or vehicle was administered 30 min prior to ischemia. Behavioural testing was initiated 7 days post ischemia and included assessment of anxiety and locomotor behavior in the elevated plus maze and open field, and fear and spatial learning in a Y-maze passive avoidance task and in the Barnes maze, respectively. Immunofluorescence served to detect BDNF and TrkB expression in the hippocampus, basal lateral amygdala (BLA), and the paraventricular nucleus of the hypothalamus (PVN) 30 days post reperfusion, and expression of markers association with neuronal injury and inflammation, including NeuN, glial fibrillary acidic protein (GFAP), ionized calcium binding adaptor (IBA1) and tumor necrosis factor α (TNFα). The data revealed improved spatial memory and fear retention in ANT-treated ischemic rats ($p < 0.01$). ANT also attenuated ischemia-induced increased and decreased BDNF and TrkB mRNA and protein levels in the amygdala and hippocampus, respectively ($p < 0.05$). The prolonged heightened BDNF and TrKB expression at the PVN also appeared influenced by CRHR1 signaling. ANT blunted post-ischemic IBA1, GFAP and TNFα-immunoreactivity in all hippocampal sub-regions and conferred neuronal protection in the CA1 and BLA ($p < 0.05$). Together, these findings suggest that CRHR1 activation upon cardiovascular insults significantly contributes to ensuing neuronal and functional changes influencing post ischemic recovery. This work was supported by a grant from the

National Science and Engineering Research Council of Canada to Dr. Hélène Plamondon and internal funding from the University of Ottawa.

20. **Dopaminergic nature of behaviorally-induced emission of 50 kHz appetitive vocalizations.** Kevin G. Mulvihill1, Stefan M. Brudzynski1, 1. Department of Psychology, Brock University, St. Catharines, ON, Canada. The 50 kHz ultrasonic vocalizations (USVs) of the rat (Rattus norvegicus) have been strongly associated with a variety of appetitive contexts of both a social and non-social nature and are believed to be driven by dopamine. The current study was set out to investigate the possible quantitative and qualitative differences in 50 kHz USVs elicited in 4 distinct behavioural contexts (2 social and 2 alimentary conditions) and to test the dopaminergic hypothesis with an antagonist challenge of haloperidol. With a mixed-factorial design 32 Long Evans rats (male) were split into four conditions (8 rats per group) with an appetitive stimulus consisting of either a common female, familiar conspecific male, fruit loop reward, or sweetened ethanol (2% solution w/v). Results indicated that exposure to a common female elicited the greatest rate of 50 kHz USV production over exposure to cage-mate, ethanol, or fruit loops. USVs/min were also higher in response to cage-mate than ethanol or fruit loops. Analysis of 50 kHz call subtype proportions indicated no difference between female and cage-mate conditions in relative proportions of 'flat' 'trill' or 'non-trill frequency-modulated' calls but a difference between social stimuli and non-social stimuli. There was a greater proportion of 'flat' 50 kHz USVs in the food condition compared to any other condition. There was also a differential effect of session: across testing sessions, there was an increase in USVs/min in the alimentary conditions only, but no change in the social conditions. Haloperidol successfully antagonized 50 kHz production highlighting the role of dopamine in behaviourally relevant call production. Results provide insight to procedures for non-pharmacological appetitive triggers for 50 kHz call production. Findings indicate that social contexts elicit a greater rate of 50 kHz emission over alimentary ones with characteristic call subtype proportions within conditions suggesting behavioural relevance of such subtypes. In summary, these non-pharmacologically elicited 50 kHz calls appear dependent on dopaminergic signaling. Supported by NSERC of Canada.

21. **The antidepressant-like effect of agmatine is associated with AMPA receptor activation and increased levels of BNDF and synaptic proteins in prefrontal cortex.** Vivian B. Neis1, Morgana Moretti2, Luis Eduardo B. Bettio1, Camille M. Ribeiro1, Priscila B. Rosa1, Filipe M. Gonçalves1, Mark W. Lopes1, Rodrigo B. Leal1, Ana Lúcia S. Rodrigues1. 1Department of Biochemistry, CCB, Universidade Federal de Santa Catarina, 88040-900, Florianópolis, SC, Brazil. 2Post-Graduate Nutrition Program, CCS, Universidade Federal de Santa Catarina, 88040-900, Florianópolis, SC, Brazil. The mechanisms underlying the effects of the fast-acting antidepressant agents, particularly the NMDA receptor antagonist ketamine, involve a burst of glutamate transmission and increased activation of AMPA receptors. This modulation is associated with BDNF release, stimulation of mTOR signaling and a consequent increase in synaptic protein translation and synaptogenesis. In order to investigate safer antidepressant agents that may elicit an antidepressant effect by a mechanism similar to ketamine, our study is focused on agmatine, a neuromodulator that has been reported to exert antidepressant-like effects, at least in part, by inhibiting NMDA receptors. Therefore, this study investigated if agmatine exerts its antidepressant-like effect in the tail suspension test (TST) through modulation of AMPA receptors, BDNF/TrkB signaling, mTOR and its down and upstream signaling targets: phosphatidylinositol 3-kinase (PI3K), PSD-95, synapsin, and GluA1. Oral administration of agmatine (0.1 mg/kg) caused a significant reduction in the immobility time of mice submitted to the TST, an effect prevented by the administration of DNQX (AMPA receptor antagonist, 2.5 µg/mouse, i.c.v.), BDNF antibody (1 µg/mouse, i.c.v.), K-252a (TrkB receptor antagonist, 1 µg/mouse, i.c.v.), LY294002 (PI3K inhibitor, 10 nmol/mouse, i.c.v.) or rapamycin (selective mTOR inhibitor, 0.2 nmol/mouse, i.c.v.). Moreover, increased immunocontents of BDNF, PSD-95 and GluA1 were found in the prefrontal cortex of mice just 60 min after agmatine administration. These results indicate that the antidepressant-like effect of agmatine in the TST may be dependent on the activation of AMPA and TrkB receptors, PI3K and mTOR signaling, and acute increase in BDNF and synaptic protein levels. The results contribute to elucidate the complex signaling pathways involved in the antidepressant effect of agmatine and point to similarities in the mechanisms underlying the antidepressant effects of

agmatine and ketamine, reported in literature, reinforcing the role of these molecular targets for antidepressant responses. Financial support: CNPq (#308723/2013-9 and 449436/2014-4), CAPES (Brazil).

22. **Loss of neuronal activity in the central amygdala of seizure prone Fmr1 KO mice is conserved across multiple mouse lines susceptible to audiogenic seizures.** Davenport MH1,2; Robinson CK1,2; Grainger LM1; King AJ1,2; Erickson CA1,2; Schaefer TL1. 1Department of Psychiatry, Cincinnati Children's Hospital Medical Center, Cincinnati OH USA; 2University of Cincinnati, Cincinnati OH USA. Fragile X Syndrome (FXS) is the most prevalent, known, single gene cause of autism and heritable intellectual disability. FXS is caused by an expanded CGG repeat in the 5' UTR of the Fragile X Mental Retardation 1 (FMR1) gene that results in its transcriptional silencing leading to neuronal hyperexcitability. Individuals with FXS experience a wide range of behavioral, intellectual, and physical abnormalities including anxiety, hypersensitivity to sensory stimuli, and an increased risk of seizures. These phenotypes are well conserved in the Fmr1 KO mouse model of FXS. Appropriate extracellular signal-regulated kinase 1/2 activity (ERK) is critical for activity dependent synaptic plasticity and appropriate behavior. ERK activation is typically associated with neuronal activity in both excitatory and inhibitory neurons. Under basal, non-challenged conditions we have shown that ERK activation is elevated in the amygdala, hippocampus and striatum of mice and in blood lymphocytes of mice and humans with FXS independent of changes in ERK total protein levels. Since it is clear that activity dependent neuronal signaling is altered in FXS, we hypothesized that ERK activation is not only altered at basal conditions but also during periods of high neuronal activity and that this dysregulation is region specific. We utilized a robust audiogenic seizure paradigm that consists of a 1 min habituation, then a 2 min 120dB priming tone, followed by 1 min of silence, and finally a second 120dB tone that induces wild running and tonic/clonic seizure behavior in ~60% of Fmr1 KO mice. When examining ERK activity immediately after AGS, we discovered a striking inactivation of ERK in the central nucleus of the amygdala (CeA), the major inhibitory output of the basal ganglia, only in mice that experience seizure. In contrast, the lateral amygdala (LA), which serves as the primary input center of the amygdala and consists of mostly excitatory neurons, becomes over activated in these same seizure mice. Based upon preliminary in situ hybridization data for the immediate early gene c-Fos we also demonstrated that these ERK effects during seizure are concomitant with elevated neuronal firing in the LA and reduced neuronal firing from the CeA in Fmr1 KO mice that seized. Further study demonstrated that the deactivation of the CeA begins during the priming phase of AGS, preceding the initiation of seizure behavior. ERK activation patterns across seizure resistant and seizure prone mice including B6 WT littermates, Fmr1 KOs, maternal Ube3a KOs (Angelman Syndrome model), and outbred CD1 mice (which are susceptible to AGS) further suggest that decoupling of neuronal activity between the lateral and central amygdalar nuclei is a key event in AGS susceptibility across genetic mutants and backgrounds. Future studies will determine if similar decoupling contributes to other amygdala dependent behavioral dysfunctions in FXS.

23. **Investigating the effects of history of concussion on baseline scores on the Sport Concussion Assessment Tool (SCAT-2).** Kim M Gerecke1, Madeline Davis1. Dept. of Psychology and Neuroscience Program, Rhodes College, Memphis, TN. Concussion is among the most common sports related injuries, and the Sport Concussion Assessment Tool (SCAT) is frequently used to assess neurocognitive changes following a concussion. However, there is little known regarding if a previous concussion affects baseline normative values in college athletes. To address this question, student athletes (age range 17 – 21) at a small, private liberal arts college were assessed for preseason baseline performance using the SCAT-2. This survey assesses 24 physical symptom complaints, such as headache, nausea, sensitivity to light or noise, etc. which are common in concussed persons, as well as the subjective rating of the severity of any indicated symptom (mild to severe). Preliminary results of a pilot sample indicate that ~39% of athletes reported having had at least one previous concussion. Preliminary results show no differences in student reports of physical symptom complaints or symptom severity. There were no differences in baseline performance in tests of orientation, immediate or delayed memory recall, performance on a digits backward test, or performance in the balance testing, between

students reporting at least one previous concussion compared to those that had no previous concussions. Continuing research will expand this data set, and investigate if there are typical clusters of symptoms reported by in students who have had a previous concussion. In addition, there is emerging evidence that there are sex differences in rates of concussion, and that females may require longer recovery times following incidence. Thus, we will also investigate possible sex differences due to concussion history in preseason baseline performance in student athletes. Importantly, as few studies of sport related concussion have been performed in high-performing students at small, private institutions, these data will help describe the effects of concussion on baseline performance across a wider range of students than are currently described in the literature.

24. **An investigation of maternal experience on neurobiological and behavioral responses in middle-aged female rats.** Kirk, E.1, Thompson, B.1, Barha, C.2, Galea, L.3, Bardi, M.1, Kent, M.1, & Lambert, K.1 1Department of Psychology and Behavioral Neuroscience, Randolph-Macon College, Ashland VA USA. 2Department of Physical Therapy and Faculty of Medicine, University of British Colombia, Vancouver, BC Canada. 3Department of Psychology and Neuroscience Program, University of British Colombia, Vancouver, BC Canada. In preparation for motherhood, several neurobiological alterations that enable female mammals to meet the energy demands associated with pregnancy, parturition, and lactation have been observed. Previously, our lab revealed that young-adult, primiparous females demonstrated more effective search strategies in a spatial memory task than age-matched nulliparous females; furthermore the primiparous females exhibited decreased glucocorticoid receptor immunoreactive cells in the CA1 hippocampus, a nonsignificant trend towards increased BDNF receptors in the CA3 hippocampus, and a higher DHEA/corticosterone ratio, all indices of effective coping and emotional regulation. Given these former findings, the current study explored problem-solving strategies and emotional resilience in middle aged (13 months), nulliparous (n =11), primiparous (n =11), and multiparous (n = 10) Long-Evans rats to provide more specific information about lasting emotional regulation in the post-lactational, maternal rat. Specifically, all rats were subjected to five days of unpredictable stress (US) and then were trained in the Dry Land Maze (DLM), a spatial learning task. Fecal samples were collected before and during US and after DLM testing so that hormones associated with stress and resilience, corticosterone and dehydroepiandrosterone (DHEA), respectively, could be assessed. Following DLM training, testing, and a probe test (to assess prediction errors), the brains were processed for mineralocorticoid receptor- and relaxin3 receptor immunoreactivity (both implicated in emotional responsiveness). Cardiac blood was collected before perfusion to assess estradiol levels via radioimmunoassay (RIA). ANOVA revealed that nulliparous females had a faster latency to reach the correct well on DLM Test day 2 ($p = 0.01$) but had significantly more errors on Test day 3 ($p = 0.04$) when compared to multiparous females. However, there were no significant differences found during DLM Probe day. In accordance with past findings, nulliparous females had significantly more fecal boli ($p = 0.02$) during a forced swim test when compared to multiparous females. Thus, although the effects of maternal experience were not as robust as observed in younger rats, reproductively experienced rats exhibited less stress responsiveness during swim stress (i.e., fewer fecal boli) and more focused responses on the last day of DLM training. Stress hormone assays and brain immunoreactive tissue quantification are ongoing and will be reported. This research was supported by the R-MC Klein-Maloney Fellowship for Women in the Sciences awarded to EK.

25. **Strains of an accompanying conspecific affect the efficacy of social buffering in male rats.** Yasushi Kiyokawa1, Kayo Nakamura1, Yukari Takeuchi1, Yuji Mori1. 1Laboratory of Veterinary Ethology, The University of Tokyo, Tokyo, Japan. Social buffering is the phenomenon in which a subject's stress is ameliorated when the subject is accompanied by a conspecific animal(s) during exposure to the distressing stimuli. We previously reported in male Wistar rats that the presence of another Wistar rat mitigates conditioned fear responses to an auditory conditioned stimulus (CS) paired with a foot shock. Subsequent analyses revealed several characteristics of this social buffering of conditioned fear responses. However, our knowledge is still limited regarding the specificity of accompanying conspecifics. In the present study, we assessed whether rats of other strains induce social buffering in Wistar rats.

When the fear-conditioned Wistar subject alone was re-exposed to the CS, it showed increased freezing, decreased investigation and walking, as well as elevated corticosterone levels. The presence of a Wistar rat, as well as a Sprague-Dawley or Long-Evans rat, blocked these behavioral and endocrine responses. In contrast, these responses were not mitigated if a Fischer 344 rat was present when the Wistar subject was re-exposed to the CS. Further, we found that the presence of a Lewis rat similarly blocked fear responses to the CS of the Wistar subject. Based on these findings, we conclude that strains of an accompanying conspecific affect the efficacy of social buffering in rats.

26. **Ketamine exposure during adolescence increases sensitivity to reward-related stimuli in adulthood.** Lace M. Riggs2, Jason B. Alipio2, Israel Garcia2, Arturo R. Zavala3, and Sergio D. Iñiguez1. 1Department of Psychology, University of Texas at El Paso, El Paso, TX. 2Department of Psychology, California State University, San Bernardino, CA. 3Department of Psychology, California State University, Long Beach, CA. Major depressive disorder (MDD) is commonly diagnosed in children and adolescents, and when left untreated, may result in negative consequences that extend into adulthood. It is estimated that children and adolescents who suffer from MDD are likely to develop conduct and anxiety disorders, and that up to 25% eventually develop substance abuse disorder. Consequently, this has resulted in a disproportionate increase in the prevalence of antidepressants prescribed to populations below 20 years of age. Recently, the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine, has been shown to alleviate symptoms of MDD in individuals that suffer from treatment-resistant depression. However, little is known about the potential long-term consequences of exposure to ketamine during early development. This is particularly important to examine, given ketamine's abuse potential. To address this issue at the preclinical level, we examined whether ketamine exposure during adolescence results in long-lasting changes in sensitivity to the rewarding effects of sucrose (i.e., natural reward), as well as cocaine (i.e., drug reward). Specifically, male c57BL/6 mice were exposed to ketamine (0 or 20 mg/kg) during adolescence (postnatal days [PD] 35-49) and were later assessed in adulthood (PD 70+) on behavioral responsivity to a sucrose solution (1%), or cocaine (0, 2.5, 5, 7.5, 10, or 20 mg/kg) place conditioning (CPP). Here we show that adult mice pretreated with ketamine during adolescence displayed enhanced preference for a sucrose solution, as well as environments previously paired with moderately low doses of cocaine, when compared to saline pre-treated controls. Together, our findings suggest that exposure to ketamine during adolescence increases sensitivity to both natural and drug-rewards, later in life. Funding: NIGMS (SC2GM109811).

27. **Prodynorphin genetic polymorphisms and ventral striatonigral pathway activity contribute to individual differences in novelty seeking and positive reward traits.** Gabor Egervari1,2, Didier Jutras-Aswad1, Joseph Landry1,2, Michael L Miller1,2, Sarah Ann Anderson1,2, Michael Michaelides1,2, Michelle M Jacobs1,2, Cyril Peter1,2, Georgia Yiannoulos1, Xun Liu1, Yasmin L Hurd1,2. 1 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029, USA. 2 Department of Neuroscience, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029, USA. Genetic factors impact behavioral traits relevant to numerous psychiatric disorders and risk-taking behaviors, and different lines of evidence have indicated that discrete neurobiological systems contribute to such individual differences. This presentation will explore the relationship of genetic variants associated with neural circuits implicated in reward and novelty-seeking traits. Specifically, we focus on the prodynorphin (PDYN) gene that is enriched in the ventral striatonigral/striatomesencephalic pathway, a key neuronal circuit implicated in positive 'Go' behavioral choice and action. Our multidisciplinary approach identified a single nucleotide polymorphism (SNP), rs2235749 that modifies striatal PDYN expression through altering the binding of miR-365, a microRNA that targets the PDYN 3'-untranslated region. The SNP is significantly associated with PDYN mRNA expression particularly in the nucleus accumbens shell (NAcSh) as well as to novelty- and reward-related behavioral traits in humans and translational animal models. We provide evidence that the Pdyn-miR365 interaction in the NAcSh directly influences novelty seeking exploratory behavior and facilitates the self-administration of natural rewards. Overall, this translational study suggests that genetically determined miR-365-mediated epigenetic regulation of PDYN expression in mesolimbic

striatonigral/striatomesencephalic circuits contributes to novelty seeking and positive reinforcement traits. The findings will be discussed in relation to individual vulnerability to addiction and related disorders. This work was funded by NIH DA15446.

28. **An open source toolkit for combining neurophysiology and rodent behavior.** Katalin Sviatkó1, Tamás Laszlovszky1,2, Panna Hegedüs1, Nicola Solari1, Joshua I Sanders3,4, Balázs Hangya1. 1 Institute of Experimental Medicine, Hungarian Academy of Sciences, Lendület Laboratory of Systems Neuroscience, Budapest, 2 Faculty of Information Technology and Bionics, Pázmány Péter Catholic University, Budapest, 3 Cold Spring Harbor Laboratory, Cold Spring Harbor, 4 The Danish Research Institute of Translational Neuroscience, Aarhus University, Aarhus. Understanding how neurons represent specific information about external stimuli and internal variables requires registering neuronal action potential firing while animals are engaged in different behaviors. The millisecond timing of neuronal firing has strong implications on the scope of such behavioral tasks. One can only hope to extract specific information carried by spike timing if behaviorally relevant events of the task, like sensory stimuli or behavioral feedback, are under the same precision of temporal control. We present an affordable, modular, open source system capable of flexible behavioral task design and execution, submillisecond precision hardware control, combined recordings and optogenetic stimulation. Key components of this system are (i) custom designed, modifiable environments for mouse behavior; (ii) open source microcontroller-based behavior control equipment; (iii) open source data acquisition system (Siegle JH, Voigts J) (iv) open source computer vision based position tracking (Lopes G); (v) open source pulse generator; (vi) light source (laser or LED) and a light coupling system for optogenetic stimulation; (vii) freely available Matlab software package. How this setup operates will be demonstrated on a simple associative learning task. We believe this system will be a useful tool for a broad community of neurophysiologists.

29. **Integrity of Parent's Brain in Infancy Supports the Development of Children's Social Competencies.** Eyal Abraham1, Talma Hendler2,3, Orna Zaggory-Sharon1; Ruth Feldman1,4. 1Psychology and Gonda Brain Research Center, Bar Ilan university, Ramant Gan, Israel; 2Functional Brain center, Wohl Institute of Advanced imaging, Tel-Aviv Sourasky Center, Tel aviv, Israel; 3School of Psychological Sciences, Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University, Tel aviv, Israel; 4Child Study Center, Yale University School of Medicine, New Haven, CT, USA. Studies in animal models demonstrate that the cross-generation transmission of mammalian sociality begins with plasticity of the parent's brain in the postpartum; such plasticity triggers expression of the species-typical parenting behaviors, which, in turn, organize infant brain and behavior to life with others. No study, however, has tested such cross-generational sequence in humans and charted its progression from integrity of the parental brain in infancy to the emergence of core social competencies in human children. We measured brain response of 45 primary-caregiving parents to their infant's stimuli, observed parent-infant synchrony, and assayed parental oxytocin (OT). Intra- and inter-network connectivity were computed in three main networks of the human parental brain - core-limbic, embodied-simulation/empathy, and mentalizing. In preschool, two key child social competencies were observed: emotion-regulation and socialization and micro-coded. Degree of network integrity in parent's brain predicted children's social outcomes, with subcortical and cortical network integrity foreshadowing mammalian-general versus human-specific competencies. Parent-infant synchrony mediated the links between connectivity of parent's embodied-simulation network and preschoolers' ability to use cognitive/executive emotion regulation strategies, highlighting the inherently dyadic nature of this network and its long-term effects on tuning young to social life. Parent's inter-network core-limbic-embodied-simulation connectivity predicted children's OT as moderated by parental OT. Our study is the first study in humans to chart longitudinal links from network integrity of the parent's brain in infancy and two critical child social skills in preschool, suggesting how the parent-infant interface provides the template for species continuity and evolutionary change via reciprocal social behavior. Our findings demonstrate how connectivity of the parent's brain in specific and specialized neural circuits profoundly affects their children's social development, predicting two key social competencies in preschoolers – emotion

regulation and socialization. Conceptually, by demonstrating the fundamental social embeddedness of the human brain, our findings challenge the solipsistic theoretical stance underpinning most current neuroscience research and may contribute to narrowing the gap between the brain of one individual and that of other social beings. We further suggest that investigation of human parenting, as the prototypical context for such embeddedness that carries profound effects for offspring's survival and thriving, functions as a complex brain-behavior-environment system.

30. **Elevated blood ketone levels increase the latency of anesthetic induction in GLUT1 mouse model.** Ari, Csilla 1; Murdun, Cem 1; Goldhagen, Craig 1; Rogers, Christopher 1; D`Agostino, Dominic1. 1Department of Molecular Pharmacology and Physiology, Hyperbaric Biomedical Research Laboratory, Morsani College of Medicine, University of South Florida, Tampa FL, USA. Ketogenic diets have been proven effective in seizure disorders and in several neurological diseases, by supplying alternative energy source to the brain in a form of ketone bodies. Elevated blood ketone levels have been considered to play a role in neuroprotection and were also suggested to lead to reduced oxygen consumption. We tested on GLUT1 deficiency syndrome mice model whether elevation of blood ketone levels would result in latency in anesthetic induction. 3-5 months old GLUT1 deficiency syndrome mice were fed by either standard rodent diet (SD), ketogenic diet (KD) or SD mixed with 20% ketone salt supplementation (SD+KS) for 10 weeks. Induction of mice to isoflurane anesthesia was video recorded. The time from closure of induction chamber lid until the last movement of mice was measured by a blinded observer. Latency to anesthesia induction was significantly increased in KD and SD+KS groups ($p=0.003$; 0.018, respectively), compared to control. This trend was the same after normalizing the results to body weight. Blood ketone levels were measured immediately after induction. Blood ketone level showed high correlation ($R=0.99$) with latency to induction. Other animal models are to be tested in the future to find out whether only blood ketone levels or other factors contribute to the increased latency to anesthetic induction.

31. **Individual differences in fear extinction; Role of orexin and cholinergic systems.** Wilson, Marlene A.; Sharko, Amanda C; Kaigler, Kris F; Mott, David; McElroy, Joshua; Hartshorn, George; Fadel, Jim R. University of South Carolina School of Medicine, Columbia SC. Post-traumatic stress disorder (PTSD) is an anxiety disorder that can develop after experiencing a life-threatening trauma, such as combat service, assault, or a natural disaster. Not everyone who experiences these types of traumas develops PTSD, suggesting that some neurobiological or hormonal factors may confer resiliency, or risk, to the long-term negative effects of traumatic stressors and extinguishing fear memories. Our laboratory has demonstrated that outbred Long-Evans rats show individual differences in several models of conditioned and unconditioned anxiety-related behaviors. Rats show considerable variation in the extinction of cue-conditioned freezing behavior, with approximately one third of each group being resistant to extinguishing freezing in response to repeated presentations of the conditioned auditory cue. These same animals demonstrate poor retention of extinction learning 48 hours and 1 week later. Analysis of neuronal activation using cFos immunohistochemistry, as well as analysis of neurochemical markers, suggest potential roles for the orexinergic and cholinergic systems in regulating these individual differences in extinction learning. In two cadres of animals, extinction resistant animals showed enhanced activation of orexin containing neurons in hypothalamus following the extinction recall trial when compared with animals showing better extinction learning. Markers of cholinergic function, including levels of M1 muscarinic receptors in the amygdala, were also correlated with levels of extinction learning. Current studies are also examining if plasma endocrine (corticosterone, neuropeptide Y) levels are correlated with these individual differences in response to predator stress, as well as using pharmacological approaches to understand the role of the cholinergic and orexinergic system in these individual differences in extinction learning. Understanding the neurobiological and endocrine responses associated with individual differences may lead to novel therapeutic targets for treating anxiety-related disorders in susceptible populations or as indicators of therapeutic response. Support: VA Merit Award 1I01BX001374 to MAW, USC VP for Research ASPIRE I (Sharko) and APSIRE II (Wilson) funding, RO1 MH063344 to MAW & JRF, and R01 MH104638 to DM.

32. **The subunit-specific role of NMDA receptors in behavioral dysfunctions evoked by traumatic event.** Laszlo Biro1,2, Eva Mikics1, Eszter Sipos1, Christina Miskolczi1, Mate Toth1, Jozsef Haller1. 1Laboratory of Behavioural and Stress Studies, Department of Behavioural Neurobiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary; 2Janos Szentagothai Doctoral School of Neurosciences, Semmelweis University, Budapest, Hungary. Traumatic life events often lead to the development of post-traumatic stress disorder (PTSD), a highly debilitating psychiatric condition with long-lasting symptomatology. Recent reports suggest that glutamatergic receptor function in limbic regions, particularly N-methyl-D-aspartate receptors (NMDAR) containing different subunits play an important role in the development of trauma evoked behavioral dysfunction. Here we investigated the effects of the general NMDA blocker MK-801 and specific NR2A, NR2B and NR2C/D subunit antagonists on the expression of conditioned fear, a frequently used model of PTSD. Rats were exposed to a single series of 3mA footshocks and were tested 1 or 28 days later to compare acute and long-lasting effects of trauma on behavior and target gene expression levels in brain areas relevant for PTSD. When re-exposed to the traumatic context, rats showed a dramatic increase in freezing behaviour (conditioned fear) compared to unshocked controls. We found that the NR2A antagonist PEAQX and NR2C/D antagonist PPDA did not affect conditioned fear responses 1 or 28 days after traumatic shock exposure. However, both MK-801 and the selective NR2B subtype antagonist Ro25-6981 significantly reduced the duration of freezing in the conditioned fear test at both time points. To uncover acute and long-lasting effects of trauma on NMDA receptor gene expression in brain areas relevant in PTSD, we performed quantititve real-time PCR measurements on tissue punches from dorsal hippocampus, medial prefrontal cortex, basolateral and central amygdala. We found that NR2A and NR2B subunit mRNA expression was increased in the medial prefrontal cortex, on the first day after the traumatic event, while only NR2B mRNA levels remained elevated 28 days after shock exposure. Both NR2A mRNA expression in the basolateral amygdala and NR2B mRNA expression in the dorsal hippocampus temporarily increased 1 day after shock exposure. According our preliminary data mRNA expression levels of the key epigenetic enzyme DNMT3a was elevated 1 day after trauma exposure in basolateral amygdala, but this effect disappeared 28 days later. Our results suggest that studying the role of glutamate neurotransmission in a subunit-selective manner opens novel opportunities for understanding the mechanisms underlying trauma-induced behavioral dysfunctions. Our findings may contribute to a better understanding of the pathomechanisms of PTSD.

33. **High fat diet induced neuroinflammation and cognitive impairment can be restored by fitohormone abscisic acid treament.** A.M. Sánchez-Pérez1, S. Sánchez*1, S. Moustafa*1, Á. Garcia-Aviles1, F.E. Olucha-Bordonau1, * equal contribution. 1. Facultad de CC de la Salud, Universidad de Jaume I, Castellón de la Plana, (Castellón). The abscisic acid (ABA) is the main phytohormone involved in abiotic stress responses. However, ABA is not a molecule exclusive from plants but it can be found in many other organisms including bacteria, fungi and animals. Interestingly, it can be synthesized and secreted by a variety of human cells. Recent studies suggest a role of ABA regulating immune response and insulin action. Many neurological diseases have an inflammatory etiology and insulin resistance is a key factor in Alzheimer disease. Taking these data together we decided to ascertain if ABA has a protective effect in neuroinflammation, and brain insulin metabolism. We chose a model of neuroinflammation that involved feeding the animals with a High Fat Diet (HFD), this model induces glucose resistance and an increase of proinflammatory markers in peripheral tissues. Experimental groups included, HDF alone; HFD with ABA; and control diet with and without ABA. We confirmed that, in our model, ABA restores glucose tolerance in HFD rats, to levels of control diets rats' levels. Behavior paradigms show that HFD impairs lightly but significantly animal memory in T-maze but not in novel object recognition. Interestingly, ABA restores the cognitive performance of HFD fed animals to control levels. We measured ABA levels in blood and brain, confirming that ABA can cross the Blood brain barrier. Moreover, ABA can curtail microglia increase induced by high fat diet, as well as a number of cytokine and other insulin resistance and inflammatory markers in hypothalamus, but not hippocampus. ABA might be proposed as a new therapeutic molecule to improve cognitive and metabolic processes associated to neuroinflammatory conditions. This work has been funded by the following grants:

Conselleria Educación, Cultura y Deporte (2015-2016) AICO/2015/042 and Pla de Promoció de la Investigació de l'UJI (2014-2017) P1.1A2014-06 to AMSP.

34. **The memory-promoting effects of estradiol and low luteinizing hormone: Possible role of brain-derived neurotrophic factor.** Thornton, Janice, Bohm-Levine, Nathaniel, Oberlin College. In a variety of species, females lose some of their memory capacity when they age or if their ovaries are removed. Concomitant with aging and ovary removal, estradiol (E) levels decrease and luteinizing hormone (LH) levels increase (due to decreased negative feedback by E) and these hormones appear to play a pivotal role in memory. Indeed, ovariectomized (ovx) female rats exhibit deficits in spatial memory and either raising E or lowering LH levels reverses these memory deficits. The present studies explored whether these hormones might act on memory via effects on brain-derived neurotrophic factor (BDNF). More specifically it was investigated whether blocking BDNF action with ANA-12, a TrkB receptor antagonist, would prevent the effects of E and low LH on spatial memory. It was also determined whether E and/or LH modulate levels of BDNF in the hippocampus. All rats were adult ovx Sprague-Dawley females. A) To examine the effects of BDNF on estradiol-induced memory, animals were either: implanted with an E capsule and injected with ANA-12 (E + ANA-12); implanted with E and injected with vehicle (E + veh); or implanted with a blank capsule and injected with vehicle (blk + veh). ANA-12 (0.5mg/kg, Sigma) or saline vehicle was injected 4-6 hours prior to behavioral testing on the Object Location Test (OLT). E + veh animals displayed improved spatial memory compared to blk + veh females. ANA-12 treatment led to a loss of spatial memory in E- treated females (E + ANA-12 vs E + veh). B) To examine the effects of BDNF on memory induced by low LH levels, LH was decreased with Antide (a gonadotropin releasing hormone receptor antagonist; 1mg/kg, Bachem). The specific groups were: injected with Antide and injected with ANA-12 (Antide + ANA-12); injected with Antide followed by vehicle injection (Antide + veh); or injected with vehicle plus vehicle (veh + veh). Results are currently being analyzed. C) To examine BDNF levels in the hippocampus, brains were collected and tissue was processed using immunohistochemistry and examined for the expression of BDNF. Both E and Antide treatment significantly increased BDNF staining in the dentate gyrus, CA1, and CA3 regions of the dorsal hippocampus of ovx rats. These data suggest that BDNF may play an important role in the mnemonic effects of both estradiol and luteinizing hormone.

35. **Do prenatally methamphetamine-exposed male and female rats differ in the effect of chronic treatment with various drugs on spatial learning?** Macúchová Eva, Hrebíčková Ivana, Ševčíková Mária, Nohejlová Kateryna, Šlamberová Romana. Charles University in Prague, Third Faculty of Medicine, Department of Normal, Pathological and Clinical Physiology, Prague, Czech Republic. Chronic drug treatment has been shown to affect brain regions which are involved in the process of learning and memory consolidation. Our previous studies demonstrated that males and females are affected differently by exposure to drugs in various forms of behavior. The aim of the present study was to investigate how chronic application of cocaine (COC), morphine (MOR), MDMA ("ecstasy"), and delta-9-tetrahydrocannabinol (THC) in adulthood affects cognitive functions of adult female and male rats. Moreover, mothers of the tested offspring were exposed to injections of MA (5mg/kg) during the entire gestation to examine, if prenatal MA exposure sensitizes animals to chronic drug treatment in adulthood. Cognitive functions of adult rats were tested as an ability of spatial learning in the Morris Water Maze (MWM). Adult male and female rats were injected daily either with COC (5 mg/kg), MOR (5 mg/kg), MDMA (5 mg/kg), THC (2 mg/kg), or SA directly after finishing the MWM testing. The test consisted of three phases: the Place Navigation test, the Probe test and the Memory Recall test. Our data demonstrated that prenatal MA exposure did not induce changes in learning or memory of adult male and female rats tested in the MWM. As far as the chronic drug treatment is concerned our results are as follows: COC weakened both learning and memory recall only in females, by increasing the distance travelled, the latency to reach the hidden platform, and the search error. In females, MDMA worsened both learning and memory recall, while males only demonstrated increased distance, latency and search error in the Memory Recall test. Additionally, in the Probe test, females after MDMA treatment swam less often across the quadrant where the platform was located. Both, THC and MOR diminished learning and

memory in females. The speed of swimming was not affected by COC treatment, on the other hand, MDMA, THC and MOR increased speed of swimming only in females. Furthermore, regardless of an adult drug treatment, males demonstrated a better ability of spatial learning compared to females. Thus, our results indicate that the adult treatment with different drugs affects the behavior of rats in a sex-specific manner. It seems that females demonstrated a higher sensitivity to the effect of chronic drug treatment of various drugs; however, the effect was seen regardless of prenatal drug exposure. Supported by: PRVOUK P34, GACR 14-03708S, GAUK 88315, SVV 2016.

36. **Rat model of prenatal malnutrition: prefrontal cortical dysfunction and neuropsychiatric implications.** Jill A. McGaughy1 and Janina R. Galler2 1. University of New Hampshire. 5. The Chester M. Pierce, M. D., Division of Global Psychiatry, Massachusetts General Hospital and Department of Psychiatry, Harvard Medical School, Boston, MA 02120, United States Worldwide malnutrition is estimated to impact approximately 1 in 4 children. Studies of adults in China as well as the Netherlands have shown an increased prevalence of neuropsychiatric disorders in adults who were exposed to famine in utero or in early childhood. Convergent evidence from long-term studies of adults exposed to malnutrition in the first year of life in Barbados also show increases in the prevalence of neuropsychiatric disorders with specific impairments in attentional, and affective processing. Parents and teacher ratings of attention confirmed impairments in childhood and adolescence, that persisted into middle adulthood as measured by self-report. Insights related to the impact on the brain of prenatal protein malnutrition have been gained through the use of a rat model of this developmental insult. The offspring of rat dams assigned to receive either a low-protein (6% casein) or high protein (25% casein) diet prior to and throughout pregnancy are fostered to well-nourished dams. Adult rats have been tested in a series of studies aimed at assessing attention and determining the neurochemical, neuroanatomical and epigenetic changes in the prefrontal sub-regions that may underlie these disruptions in attentional processing. Over several studies, we have found that rats exposed to prenatal protein malnutrition (6/25) show cognitive rigidity in tests of attentional set shifting and distractibility when compared to control subjects (25/25) recapitulating attentional impairments found in the Barbados Nutrition Study. We have also found diet-related changes in prefrontal noradrenergic innervation of the region, monoaminergic neurochemistry, decreased metabolic activity and perturbations in KCNJ3 (GIRK1). These data support the hypotheses that that attentional impairments produced by malnutrition persist across the lifespan, and that these impairments arise from disruptions to the inhibitory/excitatory balance in the prefrontal cortices. Support NIH MH074811 (JRG) HD060986 (JRG).

37. **Acute amphetamine administration improves attention in rats with low baseline performance.** Turner, K.M.1, Peak, J.1 and Burne, T.H.J. 1,2. 1Queensland Brain Institute, The University of Queensland, St Lucia, QLD, Australia. 2Queensland Centre for Mental Health Research, Wacol, QLD, Australia. Psychostimulants, such as amphetamine, are widely used to treat attentional deficits. However, few studies have demonstrated procognitive effects of amphetamine in rodents. In humans, response to dopaminergic medications is complex and task dependent with improvement often dependent on baseline performance. Here, our goal was to determine if poor attention in rats could be improved following low dose of amphetamine. We then examined the relationship between baseline performance, drug response and catecholamine levels in corticostriatal tissue. Rats performed a signal detection task with varying signal durations before systemic administration of saline, 0.1 or 0.25mg/kg amphetamine (N=18). Neurochemical analysis of catecholamine levels was performed on the prefrontal cortex (PFC) and dorsal striatum (CPU). Reducing the signal duration impaired accuracy, providing a performance window in which accuracy could improve or worsen. Following 0.1mg/kg amphetamine, accuracy in poor performing individuals increased to that seen in high performing rats. Furthermore, baseline accuracy correlated negatively with the magnitude of improvement after amphetamine across all rats. CPU homovanillic acid (HVA) levels were increased in poor performers and were also negatively correlated with performance. No changes were found in the PFC. These results indicated poor performance was associated with greater response to amphetamine and altered CPU DA metabolism. In humans, response to amphetamine is hypothesised to occur via an inverse U-shaped relationship

between prefrontal DA and performance. However, these results suggest the balance between cortical and striatal DA levels may be fundamental to explaining individual differences in response to psychostimulants.

38. **Dorsal hippocampal dopamine D2-type receptors sex-specifically mediate the social transmission of food preferences in mice.** Richard Matta1, Emily A. Underwood1, Zoe K. Leach1, Alex C. Vertes1, Victoria Atabakhsh1, Mayara B. da Silva1, Elena Choleris1. 1Department of Psychology and Neuroscience Program, University of Guelph, Guelph, ON, Canada. Dopamine (DA) is involved in the regulation of motivationally relevant behaviors including drug/alcohol addiction, food intake and social behavior. With systemic treatments, our lab has previously found that D1-type receptors (D1/D5) mediate social learning, whereas D2-type receptors (D2/D3/D4) mediate food intake in the social transmission of food preferences (STFP) in mice (Choleris et al, 2011). Yet, it remains unclear which brain region(s) underlie these effects. The ventral tegmental area has dopaminergic projections to various limbic brain regions, including the nucleus accumbens, amygdala, and hippocampus. In particular, the hippocampus expresses both DA receptor families, and is involved in the regulation of the STFP in rodents. We have previously found that dorsal hippocampal D1-type receptors mediate social learning in the STFP in both male and female mice (Matta & Choleris, 2014). In this study, we investigated the role of dorsal hippocampal D2-type receptors in the STFP. To do this, we microinfused the DA D2-type receptor antagonist Raclopride (at 10, 14, 18 or 20 µg/µL) directly into the dorsal hippocampus of adult male and female CD-1 mice 10 minutes before a social interaction where mice had the chance to learn a socially transmitted food preference from a same-sex conspecific. We found that the lowest dose (10 µg/µL), and two highest doses (18 and 20 µg/µL) of Raclopride blocked social learning in female mice. The social learning impairment in females was also not secondary to changes in feeding behavior since total consumption was unaffected by Raclopride. Interestingly, intrahippocampal Raclopride had no effect on social learning in male mice. An olfactory discrimination task showed that females microinfused with the two highest doses (18 and 20 µg/µL) of Raclopride that blocked social learning, can discriminate between the two foods used during the choice test in the STFP. Thus, the social learning impairment could also not be directly explained by any changes in olfaction. Our results suggest that female sex hormones may affect the hippocampal D2-type receptor mediation of social learning. Such effects on females are in agreement with the estrogenic regulation of the DA system and the STFP (see Ervin et al, 2015). The role of dorsal hippocampal D2-type receptors in various social and nonsocial behaviors during the social interactions will also be highlighted. Supported by NSERC.

39. **Gender Differences in Decision-Making under Risk.** Cherkasova M. V.1, Winstanley C. A.2, Clark L. 2, Stoessl A.J. 1. Pacific Parkinson's Research Centre, Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC, Canada 1. Department of psychology, University of British Columbia, Vancouver, BC, Canada 2. Women are more risk-averse than men across a number of real-life contexts, including financial decision-making. However, gender differences have not been reliably detected on laboratory tasks involving cost-benefit decision-making under risk, and the cognitive mechanisms that underlie gender differences in risk-proneness remain incompletely understood. Some prior evidence suggests differential sensitivity to the prospects of winning and losing for males versus females. We examined performance of male and female participants on the Vancouver Gambling Task (VGT) structured as a series of gambles allowing to derive individual psychometric functions for risk tolerance and to model choice behaviour under prospect theory for each participant. In each, trial participants choose between a less probable prospect of winning a larger amount of money and a more probable prospect of winning a smaller amount. The task was performed both in a win frame (described above), and in a loss frame, where choices are made between a more probable smaller loss and a less probable larger loss. Participants' electrodermal activity (EDA) was recorded during task performance. We found that in the win phase of the task female participants were more risk-averse than male participants ($p=0.008$), and the value function under Prospect Theory for male participants was steeper than for female participants ($p = 0.02$). Decision parameters did not differ significantly between males and female participants on the loss phase of the task. In the win phase, feedback-related EDA was

significantly higher for male relative to female participants (p=0.01). There were no significant differences between the genders in the loss phase. This suggests that higher risk proneness in men relative to women may be related to higher arousal they experience in the context of winning.

40. **Exploring Neurobiological Markers of Resilience Through Life's Ups and Downs: Effects of Contingency Training in Male and Female Long-Evans Rats**. Kent Molly, Scott Samantha, Mckearney Noelle, Dozier B, Lambert Skylar, Terhunecotter Brennan, Kirk Emily, Thompson Brooke, Bardi Massimo, & Lambert Kelly. Department of Psychology and Behavioral Neuroscience, Randolph-Macon College, Ashland VA USA. Despite the availability of pharmacological treatments, depression rates continue to rise in our society; with females twice as likely to receive a diagnosis as males. In contrast to learned helplessness models of depression, effort-driven reward (EDR) training strengthens associations between effort and rewards, leading to increased persistence in tasks associated with uncertainty. Consequently, EDR training serves as a model for investigating behavioral strategies offering protection against depressogenic symptoms. In the current study, male (n=16) and female (n=18) Long Evans rats were assigned to contingent (daily digging for food reward) or non-contingent (no requirement for reward) groups during 6 weeks of EDR training (n=8 or 9 for each group), followed by 10 days of chronic unpredictable stress (CUS). Subsequently, rats were assessed in two cognitive tasks: an unsolvable task to assess persistence and a dry land maze (DLM) to assess learning, including a probe trial, responses to prediction errors. Results indicated that, during the CUS forced swim, females exhibited significantly higher float durations whereas males exhibited increased frequency of controlled sink responses, both indicative of energy conservation. Males also had increased rates of head shakes, a potential recalibration response, whereas females had increased attempts to escape the tank. Endocrinological assays conducted on fecal samples collected during CUS indicated that contingent rats, regardless of sex, exhibited significantly higher DHEA/CORT ratios (viewed as adaptive) than non-contingent rats. Additionally, a sex by contingency interaction indicated that contingent males and non-contingent females approached the unsolvable stimulus more often than the other groups; however, no differences in latency to approach the stimulus were observed. In the probe trial, contingent rats exhibited significantly more rearing responses, enabling increased environmental processing, than non-contingent animals. One hour following the probe trial, brains were processed for immunocytochemistry for several proteins in relevant brain areas. No effects were observed in cFos expression in the lateral habenula, paraventricular nucleus of the thalamus, basolateral amygdala, insular cortex or retrosplenial cortex. No effects were observed in hippocampal GFAP or doublecortin. Thus, in the current study, males and females responded differently to stressful and uncertain situations, confirming the importance of including both sexes in these investigations. Additionally, contingency training resulted in more resilient hormone responses to CUS, suggesting that EDR training influences various measures of resilience, serving as a valuable tool for investigating the efficacy of behavioral treatment strategies for emotional disorders. Work supported by NIMH award 1R15H101698-01A1 to KGL.

41. **Resilience Therapy for Depression: Exploring Neurobiological Adjustments to Predisposed and Acquired Behavioral Strategies.** 1McKearney, N., 1Dozier, B., 1Lambert, S., 1Scott, S., 1Kent, M., 1Bardi, M., & 1Lambert, K. 1Department of Psychology and Behavioral Neuroscience, Randolph-Macon College, Ashland VA USA. The prevalence of depression in today's society continues to rise, despite a multi-billion dollar antidepressant pharmaceutical industry. Consequently, it is important to consider alternative therapeutic strategies such as relevant lifestyle and neurobiological factors. Accordingly, the purpose of this study was to assess how effort-based reward training (acquired behavioral strategies) and coping strategy (predisposed behavioral strategies) impact the amount of beta-catenin expression, recently implicated in emotional resiliency (ref) in the dentate gyrus of the hippocampus, as well as additional behavioral and neurobiological indices of resilience. After determining the individual coping strategies (passive, active, or flexible) of 30 male Long-Evans rats, animals were exposed to effort-based reward training, with half assigned to a contingent group that had to exert effort (dig) to gain a food reward (Froot Loop pieces) while the other half were assigned to a non-contingent group yoked to contingent rats receiving a food reward regardless of effort exerted. Subsequently, all rats were exposed

to a problem-solving resiliency task. The animals were then exposed to one week of repeated unpredictable stress (RUS) during which behavioral stress responses to forced swim were observed. Following RUS, brains were processed for beta-catenin and doublecortin-immunoreactivity (DCX; a marker of neuroplasticity) in the dentate gyrus. Results suggested that, although contingency training failed to increase persistence in the resiliency task as predicted, contingent animals exhibited less immobility during the first swim assessment; further, an interaction was observed with head shake responses during swim (thought to be associated with emotional regulation). Contingent animals increased their floating duration during the second swim, whereas the non-contingents decreased float duration. Considering that floating conserves energy, this effect is viewed as an adaptive response during the swim task (Lambert et al., 2014). Regardless of contingency training, coping strategies had no effect on the observed behavioral measures. Further, neither coping nor training influenced beta catenin-immuoreactivity; however, passive copers had significantly more DCX expression than the other two coping styles. In contrast to our previous work with contingency training and coping strategies, the addition of RUS resulted in fewer effects in the current study. Although a few behavioral indices of emotional regulation were observed in flexible copers, the neurobiological effects weren't as robust. Hence further research needs to be conducted to determine the impact of varying durations of stress on neurobiological outcomes. Work supported by NIMH award 1R15H101698-01A1 to KGL.

42. **The impact of neurogenesis on flexible maze training: effects on hippocampal volume and cognition.** Timothy Schoenfeld1, Diane Rhee1, Heather Cameron1. 1Section on Neuroplasticity, National Institute of Mental Health. Previous research has shown that taxi cab drivers in London have larger hippocampi than non-drivers, suggesting that intense spatial training influences hippocampal growth. In addition, ablation of neurogenesis in adult rats reduces hippocampal volume, therefore we were interested in devising a rat-model of spatial-training induced hippocampal growth and exploring the effects of ablating neurogenesis on that model. To do so, we created a new maze environment, called the flex maze, a standard labyrinth with removable walls to create multiple maze environments within the same arena. We treated GFAP-TK transgenic rats and WT littermates with valganciclovir beginning at 8 weeks of age to inhibit adult neurogenesis. Rats were then trained on three different maze configurations, each with unique olfactory and visual cues, over the course of 4 weeks, were tested on an object location task, and perfused to measure hippocampal volume using a 14.1T MR scanner. Both WT and GFAP-TK rats learned various mazes at the same rate, showed spatial knowledge of the mazes in probe trials, and accurate retrieval of different mazes after all mazes had been learned. Only the maze scented with peppermint, an aversive odor for rats, showed a genotype difference, as WT rats were slower to solve this maze when switched onto it and did not retain it in subsequent retrieval trials. GFAP-TK rats had smaller hippocampi than WT controls, with significant volume decreases in the dentate gyrus and CA3. Maze-trained WT rats had larger hippocampal volumes than controls, which was fully explained by growth in ventral sections of CA1. GFAP-TK rats did not show this volume increase. In an object location task, only maze-trained WT rats showed significant object location learning, whereas all control rats and maze-trained GFAP-TK rats displayed no learning. The data suggest that both neurogenesis-intact and neurogenesis-deficient rats learn multiple spatial environments just as well, even though learning in rats without neurogenesis are not affected by aversive odors like WT controls. This spatial learning does induce growth in ventral CA1 and has positive cognitive influences in WT rats, but rats without neurogenesis do not display the volume and cognitive benefits of spatial training.

43. **Exploring the Causal Link Between Ultrasonic Vocalizations and Behavior in Rats**. Candace Burke1 , Theresa M. Kisko2 , Sergio M. Pellis1 , David R. Euston1 1 Dept 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 but the calls tend to be significantly more diverse. In fact, it has been suggested that there are as many as 14

distinct call types. To date, no detailed study of the specific behavioral correlates of these many different call types has been published. The goal of our study is to determine the specific behavioral context leading to each call type. Our first study looked at vocalizations from single animals while they were expecting play, a situation associated with a large number of 50kHz calls. Using simultaneous video and audio recordings, we manually coded the exact time of occurrence of every behavior and every vocalization. A Monte-Carlo shuffling procedure was used to identify vocalization behavior correlations that were statistically significant. We found that active behaviors such as walking, running and jumping were strongly correlated with vocalizations while resting, exploration and rearing where not. Walking was strongly associated with calls including a trill while running and jumping were more strongly associated with calls made up of multiple components, including flats and blips. Our second study involved pairs of rats, one vocal and one devocalized, engaged in playful interactions. Again, we found specific calls tied to specific behaviors, with more vocalizations during active states versus exploration and rest. In general, we found that the initiator of the behaviors tended to be the one vocalizing. Following, chasing, and nape attacks were strongly associated with vocalizations when the vocal rat was the protagonist rather than the recipient. Active attempts to escape being pinned were also associated with specific calls while passive behavior was not. These results indicate that specific calls are emitted during particular moments during both exploration and during social interactions, suggesting that they serve a role in coordinating sequences of action. Supported by NSERC (Discovery Grant) and Alberta Innovates Health Solutions.

44. **Wogonin attenuates hippocampal neuronal loss and cognitive dysfunction in trimethyltin-intoxicated rats.** SUNYOUNG LEE1, BOMBI LEE2, INSOP SHIM1,2, HYEJUNG LEE2 AND DAE-HYUN HAHM1,2, 1The Graduate School of Basic Science of Korean Medicine, College of Korean Medicine, Kyung Hee University, Seoul, 130-701, Republic of Korea. 2Acupuncture and Meridian Science Research Center, College of Korean Medicine, Kyung Hee University, Seoul, 130-701, Republic of Korea. The purpose of this study was to examine whether Wogonin (WO) improved hippocampal neuronal activity, and behavioral alterations, and cognitive impairments, induced in rats by administration of trimethyltin (TMT), an organotin compound that is neurotoxic to the animals. The ability of WO to improve cognitive efficacy in rats rendered neurodegenerative by TMT was investigated using passive avoidance test and Morris water maze test, and employing immunohistochemistry to detect components of the acetylcholinergic system, brain-derived neurotrophic factor (BDNF) and cAMP-response element-binding protein (CREB) expression. Rats injected with TMT showed impairments in learning and memory and daily administration of WO improved memory function, and reduced aggressive behavior. Additionally, administration of WO significantly alleviated the TMT-induced loss of cholinergic immunoreactivity, and restored the hippocampal expression levels of BDNF and CREB proteins and their encoding mRNAs to normal. The findings thus suggest that WO might be useful as a new therapeutic drug for treatment of various neurodegenerative diseases.

45. **Relaxin-3/RXFP3 signalling and anxiety: effects of chronic rAAV expression of an RXFP3 agonist peptide in ventral hippocampus.** Valeria Rytova1,2, Despina E. Ganella1,2, David Hawkes1, Ross A.D. Bathgate1,2, Sherie Ma1,2, Andrew L. Gundlach1,2. 1The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia, 2Florey Department of Neuroscience and Mental Health, The University of Melbourne, Parkville, Victoria, Australia. Relaxin-3 is a peptide expressed by GABAergic neuron populations in nucleus incertus, pontine raphe and periaqueductal grey, that preferentially activates a Gi/o-protein-coupled receptor, RXFP3. Relaxin-3 neurons are stress-responsive and constitute a conserved ascending network in rodent and primate brain, with strong projections to limbic areas involved in stress, arousal and emotion-related behaviours, such as hypothalamus, extended amygdala, ventral hippocampus (vHipp) and prefrontal cortex. In rats, relaxin-3/RXFP3 signalling has been demonstrated to modulate arousal, feeding, sucrose/alcohol seeking, and depressive-/anxiety-like behaviours [see Ma S, Gundlach AL, J Neuroendocrinol 27, 457-67]. This study aimed to further characterize the effects of RXFP3 signalling in key limbic regions on ‘affective’ behaviours in the rat, such as innate anxiety and avoidance. An adeno-associated viral (AAV) vector that drives local secretion of an RXFP3 agonist, R3/I5 [Ganella DE et al., Gene Ther 20, 703-16], was bilaterally injected into vHipp of adult male, Sprague-Dawley rats (n=7-10/group). Chronic vHipp RXFP3 activation for >4 weeks

increased anxiety-like behaviours, as reflected by decreased time spent (p=0.012) and distance travelled (p=0.009) in the open arms of the elevated plus maze; and decreased time spent (p=0.0001) and distance travelled (p=0.003) in the aversive light zone of the light-dark box, compared to control. Furthermore, vHipp-R3/I5 rats exhibited significantly decreased social approach (p=0.02), social follow (p=0.01) and social sniff (p=0.01) in response to interaction with a stranger conspecific rat, compared to control. In ongoing studies we are assessing EEG recordings and key neurochemical indices in the presence and absence of vHipp RXFP3 activation. Our data suggest chronic vHipp RXFP3 activation promotes anxiogenic behaviour and avoidance. Future studies will characterize the impact of this novel neuropeptide/receptor system on the neural circuits associated with these complex behaviours to provide a better understanding of the neurochemical basis of anxiety/mood disorders, with clear implications for identifying novel therapeutic targets. Supported by NHMRC (Australia) and The University of Melbourne.

46. **The putative lithium-mimetic ebselen reduces impulsive action but not impulsive choice.** Chris Barkus1,2, Jacqueline-Marie Ferland2, Wendy Adams2, David Bannerman1, Catherine Winstanley2, Trevor Sharp1. 1University of Oxford, UK. 2University of British Columbia, Vancouver, Canada. Lithium remains the frontline treatment for bipolar disorder despite its poor tolerability and plethora of side effects due to a lack of effective alternatives, particularly in reducing suicidal behaviour. Lithium is also effective at reducing other impulsive behaviours such as pathological gambling. The mechanism by which lithium exerts its clinically desirable effects is unknown, but the best candidate is its blockade of inositol monophosphatase (IMPase), a key enzyme in the second messenger system of Gq-coupled metabotropic receptors such as the 5-HT2 family of 5-HT receptors. 5-HT2A and 5-HT2C receptors have been shown to have powerful and reciprocal effects on impulsive behaviour, with increases in 5-HT2A-mediated activity leading to increased impulsivity and, conversely, greater 5-HT2C-mediated activity leading to reduced impulsivity. Ebselen has been identified as a selective blocker of IMPase activity and may therefore act as a functional antagonist to 5-HT2A receptors and so reduce impulsivity in a manner similar to lithium. Ebselen was identified from a screening of drugs that have previously been in Phase III clinical trials and is therefore known to be well tolerated in humans. If ebselen can be demonstrated to effectively reduce impulsivity preclinically it would advance its candidacy as a safer alternative to lithium in the treatment of bipolar disorder and other impulsive control disorders. We tested acute doses of ebselen administered ip. one hour before testing in several models of impulsivity and decision-making in rats. This included the 5 choice serial reaction time task (5CSRTT), an attentional test that allows for the measure of impulsive responses, delay discounting as a test of impulsive choice behaviour, and the rodent gambling task (rGT). Furthermore, we assessed the ability of ebselen to block “wet dog shakes” induced by the 5-HT2A agonist 2,5-Dimethoxy-4-iodoamphetamine (DOI). We found that ebselen reduced premature responding in both the 5CSRTT and rGT, the principle measure of impulsive action in both tasks. However, ebselen had no effect on choice behaviour in either the rGT or delay discounting tasks. Ebselen effectively blocked DOI-induced shakes, a behavioural measure of 5-HT2A receptor activity. Collectively, these data suggest ebselen may be effective in reducing impulsive behaviour clinically and that this may be due to functional inhibition of the 5-HT2A receptor. This work is funded by the UK Medical Research Council.

47. **The activation and blockage of crf type 2 receptors of the medial amygdala alter elevated t-maze inhibitory avoidance, an anxiety-related response.** Viana, Milena B.1; Alves, Stephanie W.E.1; Portela, Natasha C.1; Silva, Mariana S.1; Céspedes, Isabel C.1; Bittencourt, Jackson C.2. 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. Previous results show that the activation of CRF type 1 (CRFR1) receptors of the medial amygdala (MeA) induces anxiogenic-like effects. The present study investigates the role played by medial amygdala CRF type 2 receptors (CRFR2) in the modulation of anxiety and panic-related responses. Male Wistar rats were administered into the MeA with the CRFR2 agonist urocortin 2 (0.5 e 1.0 µg/0.2 µl, experiment 1) or with the CRFR2 antagonist astressin 2-B (60 ng/0.2 µl, experiment 2) and 10 min later tested in the elevated T-maze (ETM) for inhibitory avoidance and escape measurements. In

clinical terms, these responses have been respectively related to generalized anxiety and panic disorder. In a third experiment, the effects of the combined treatment with urocortin 2 (1.0 µg /0.2 µl) and a sub-effective dose of astressin 2-B (30 ng/0.2 µl) were also investigated. All animals were tested in an open field, immediately after the ETM, for locomotor activity assessment. Results showed that urocortin 2, in the highest dose administered (1.0 µg/0.2 µl), facilitated ETM avoidance, an anxiogenic-like effect. Astressin 2-B, also in the highest dose (60 ng/0.2 µl), significantly decreased avoidance latencies, an anxiolytic-like effect. The lower dose of astressin 2-B (30 ng/0.2 µl) did not induce anxiolytic-like effects but was able to counteract the anxiogenic-like effects of urocortin 2. None of the compounds administered altered escape responses or locomotor activity measurements. These results suggest that CRFR2 in the medial amygdala, as CRFR1, selectively modulate an anxiety-related response. Financial funding: FAPESP and CNPq (Brazil).

48. **A gene x environment mouse model of switching between affective states: Reducing DAT function results in hypersensitivity to seasonal photoperiod-induced changes in affect.** Zackary A. Cope, Davide Dulcis, Jared W. Young. University of California San Diego, Department of Psychiatry. Bipolar disorder (BD) is a debilitating mental illness characterized by chronic relapse and switching between extreme moods. Left untreated, affected individuals experience switches between depressed mood (sadness, anhedonia, amotivation, suicidal thoughts), and mania (euphoria, impulsivity, risky behavior, reward seeking). While mechanisms underlying unipolar symptoms are relatively well understood, mechanisms underlying switches between the two extremes remain unknown. The key to understanding BD relies on identifying mechanism(s) driving switches between these two extremes in behavior within the same subject. Neurotransmitter switching between somatostatin (SST) and the dopamine synthesizing enzyme tyrosine hydroxylase (TH) has been observed in a population of rodent paraventricular hypothalamic (PaVH) neurons. This switch resulted from exposure to short-active (SA, 19 hrs light:5 hrs dark) and long active (LA, 5 hrs light:19 hrs dark) photoperiods respectively. Each condition was associated with one of two dichotomous behavioral profiles. Specifically, LA photoperiod increased TH expression in PaVH cells, inducing maniarelevant behavior, while SA photoperiod increased SST expression in these same cells resulting in elevated CRF levels and depression-relevant behavior (Dulcis, et al. Science, 2013). This observation is noteworthy because seasonal variations in day-length have been linked to relapse vulnerability in BD patients (Berk, et al. Acta Psychiatr Scand. 2007). Further, a 40% reduction in dopamine transporter (DAT) expression has been measured in euthymic BD patients (Anand, et al. Bipolar Disorders, 2011), which may represent a mechanism by which seasonal variations in day-length induce extremes in affect. Here, we exposed mice with an ~50% reduction in DAT expression (DAT-HY) to SA or LA photoperiods to assess the degree to which these manipulations can induce dichotomous behavior. Increased depression-relevant forced-swim immobility was observed in mice housed under SA conditions ($F(2,64),=4.3$, $p<0.05$), while LA photoperiod was resulted in increased mania-relevant open arm exploration ($F(2,61)=4.7$, $p<0.05$). These effects were exaggerated in DAT HY mice, consistent with preliminary findings. DAT-HY mice also exhibited hyperactivity across multiple dependant measures in the behavioral pattern monitor, regardless of photoperiod state. Further, we performed a multi-dimensional behavioral characterization in these same mice following exposure to altered photoperiods including cross-species relevant measures of feedback related decision making, reward learning, effortful motivation, and sensory processing. These results, the extent to which they recapitulate a BD relevant profile in each illness phase, associated immunohistochemical switching, and how they relate to treatment development, will be fully discussed. This study was funded by NIH R01 MH104344.

49. **Adaptations of the dorsal raphe in a rat model of depression and following antidepressant treatment.** Jessica A Babb1,2, Sofia E Linnros1,3, Kathryn G Commons1,2. 1Children's Hospital Boston, Department of Anesthesiology, Perioperative, and Pain Management, Boston, MA. 2Harvard Medical School, Department of Anesthesia, Boston, MA. 3Uppsala University, Programme in Pharmacy, Uppsala, Sweden. Serotonin (5-hydroxytryptamine; 5-HT) is strongly implicated in stress-related mood disorders such as depression and anxiety. One hypothesis of depression postulates that down-regulation

of the 5-HT1A auto-receptor is responsible for the therapeutic actions of selective serotonin reuptake inhibitors (SSRIs), but this theory is also proposed for the etiology of depression. One possible explanation for this apparent paradox is that serotonergic neurons of the dorsal and median raphe nuclei (DR and MR), which are highly organized and provide widespread innervation to the forebrain, are topographically altered in a depressed state, and that SSRIs act to reverse this topographic dysfunction. To test this idea, we utilized maternal separation in rats as an animal model of depression compared to undisturbed control-raised litters. When animals reached adulthood, rats received injections of the SSRI fluoxetine (FLX) or vehicle for 14 consecutive days. On the 15th day, activation of 5-HT neurons in response to an acute stress (15 min forced swim) was quantified in 8 sub-regions of the DR and MR by immunolabeling of c-Fos and tryptophan hydroxylase proteins. Unexpectedly, swim stress induced activation of similar numbers of 5-HT neurons throughout the raphe of maternally separated and control rats in vehicle-treated animals. In contrast, prior antidepressant treatment dramatically suppressed activation of 5-HT neurons in all sub-regions examined in both maternally separated and control rats in response to stress. The dampening effect of FLX was not due to impaired 5-HT1A auto-receptor function in the raphe, as acute injection of the 5-HT1A receptor antagonist WAY-100635 (WAY) just prior to forced swim in FLX-treated rats restored stress-induced activation of 5-HT neurons to the level of vehicle-treated rats. Interestingly, maternally separated rats appeared more sensitive to WAY treatment following antidepressant administration, leading to hyperactivation of 5-HT neurons to stress, particularly in the rostral DR of these rats. Furthermore, the number of 5-HT1A receptor binding sites in the raphe as measured using receptor autoradiography was not affected by early life experience, suggesting the 5-HT1A receptor is not desensitized in maternally separated animals. Functional consequences of both maternal separation and SSRI treatment on 5-HT1A receptors are being furthered investigated using an agonist-stimulated GTPγS assay. These results indicate complex interaction effects of prior experience and antidepressant treatment on adaptations of the dorsal raphe and 5-HT neurotransmission in response to stress. Supported by NIH Grants R01DA021801 (KGC) and F32MH108247 (JAB).

50. **Exposure to a selective-serotonin reuptake inhibitor (SSRI) during pregnancy impacts sensitization to cocaine in a sex-dependent manner.** Kott, J. M.,1 Mooney-Leber, S. M.,1 Perrine, S.,1 & Brummelte, S.1. 1Wayne State University, Detroit, MI. Each year, an estimated 13% of pregnant women are on anti-depressant medication despite suggestions in existing research of negative effects on the development of the offspring. To investigate the impact of antidepressant exposure during pregnancy in an animal model, this study utilizes female Sprague-Dawley rats that were treated with corticosterone before pregnancy to achieve a depressive-like phenotype, followed by the administration of sertraline, a commonly prescribed selective serotonin-reuptake inhibitor (SSRI) during pregnancy. Our previous results revealed altered serotonin levels in neonatal pups that were exposed to sertraline in specific brain areas. In the current study, we were interested in the propensity for substance abuse in adult animals that were prenatally exposed to sertraline. For this, adult male and female offspring were tested for alterations in locomotor behavior in a cocaine sensitization task. Animals were exposed to a daily injection of 15 mg/kg of cocaine and monitored for a one-hour testing session over the course of eight days. Preliminary results show that locomotor activity varied in a sex-dependent manner in this task. This data suggests that prenatal SSRI exposure may lead to changes in the serotonergic system that may differentially impact animals of different sexes in their responsiveness to drugs of abuse.

51. **Individual variability in mice' response to lithium: a hurdle or an advantage?** Itamar Ezer1 Catherine Belzung2 Haim Einat1,3,4. 1School of Behavioral Sciences, Tel Aviv-Yaffo Academic College, Tel-Aviv; 2INSERM 930 & Department of Neurosciences Université François-Rabelais de Tours ; Dept. of Clinical Biochemistry and Pharmacology, Ben-Gurion University of the Negev, Beersheba; 4College of Pharmacy, University of Minnesota, Duluth MN. Individual variability in response to mood stabilizing drugs poses a significant hurdle in the treatment of bipolar patients. There is a well-known heterogeneity in the response of patients to treatment and many patients are partial or non-responders. Differences in response might be related to genetics but to date specific findings are inconclusive. Accordingly, animal models may be one important venue to advance the study of individual variability in response to drugs.

Individual variability in animal models is well noted in all contexts of research and had been studies mostly in the context of animal physiology and ecology. Yet, in studies related to disease and treatment individual variability is usually treated as a limiting factor and is dealt with by standardization and by increasing the number of animals per group. Although the general tendency is to try and overcome variability, it is also possible to utilize heterogeneity in animals to explore the biology of individual variability in humans. In that context, initial work in our laboratory clearly demonstrates the heterogeneity in mice response to lithium in both models of depression and mania. Our data show that similar to patients, about one third of mice show strong response, about one third show intermediate response and about one third show no response to chronic drug administration. These diverse effects are demonstrated in both ICR and black Swiss mice. Current work in the lab is aimed at exploring physiological, biochemical and molecular correlations to the behavioral responses to lithium. Such correlations may support the attempts to predict response in models and possibly in patients and advance the development of personalized medicine in bipolar disorder. Subdiaphragmatic vagotomy does not influenced rats' behavior in elevated plus maze and does not protect against noradrenergic responses after i.p. LPS injection. Marek Wieczorek1, Anna Kobrzycka1, Krystyna Koziec2, Artur H. Swiergiel3, Marta Siudak3 1Department of Neurobiology, Faculty of Biology and Environmental Protection, Univ. of Lodz, Poland, 2University of Agriculture in Krakow, Department of Animal Physiology And Endocrinology, Krakow, Poland, 3Biol., Univ. of Gdansk, Gdansk, Poland. Peripheral administration of gram-negative bacteria endotoxin - lipopolysaccharide (LPS) is known to activate the hypothalamo-pituitary adrenal axis and brain noradrenergic systems. We studied the vagotomized rats responses to peripherally administered LPS using the HPLC-ED to measure the concentration of noradrenaline and their metabolite MHPG in various brain regions. Rats were submitted to subdiaphragmatic vagotomy and after 30 days we used them for experiments. They were injected with saline and LPS (10 µg i.p.) in random order, two hours after injection they were also in random order submitted to 5 min. elevated plus maze test (EPM), and then euthanized. Their brains where removed from the skull and we isolated the hypothalamus, amygdala, prefrontal medial cortex, hippocampus, periaqueductal gray matter and the brainstem. Future chromatographic analysis indicate, that subdiaphragmatic vagotomy did not protect against increase of noradrenaline concentration in analyzed brain regions. In case of LPS injected animals we observed increased noradrenaline concentration versus saline injected ones. These results were comparable with those observed in sham operated rats. We did not observed any significant differences in animals activity in EPM, expressed as ratio of open arms/total time activity, although in case of vagotomized rats treated with LPS, this parameter was reduced. The results suggest that there may be compensatory mechanisms, responsible for transferring of immune signal to the brain, and developed during such a long time of recovery after subdiaphragmatic vagotomy. Supported by National Science Center, Poland, UMO-2012/07/B/NZ4/00205

52. **Changes of neuronal plasticity in the hippocampus of mothers induced by 3h pups separation during the first two weeks after birth.** Mostallino, Maria Cristina1; Biggio, Francesca2; Boi, Laura2; 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. The postpartum period, in all mammalian species, is characterized by dramatic changes in hormones levels, alterations in neural plasticity, including neurogenesis and dendritic remodelling in different brain areas. All the mentioned changes are believed to be a crucial prerequisite for both the proper fetal and neonatal development as well as the physiology and menthal health of the mother. Thus, while increased calmness and attenuated stress responsivity are common features of the pregnancy, the postpartum period represents a time of increased susceptibility and vulnerability to stress. Several risk factors for stress-induced mental disorders are known, but their aetiology remains still poorly understood. The aim of the present study was to evaluate the effects of repeated stress during lactation, induced by maternal separation (3h a day from 3rd to the 15th day after birth), on dendritic spine density and morphology, dendritic plasticity and cell proliferation in the dentate gyrus of mothers hippocampus. The mothers were sacrified the day of the weaning, 21 days after delivery. As expected in the hippocampus of non-stressed mothers we found a marked increase in the dendritic spines density, mushroom spines

density, dendritic lenght and dendritic branch points and a decrease of neurogenesis when compared to nulliparous female rats. Although dendritic spines density is not significantly altered, the hippocampus of stressed mothers exhibits structural alterations characterized by a different dendritic spine morphology, decreased dendritic lenght, reduced dendritic branch points. Finally, in the hippocampus of stressed mothers there was a reduction of neurogenesis respect to the hippocampus of mothers never separated from their pups. This study suggests that during the postpartum period, the hippocampus is highly vulnerable to the effects of stress. This conclusion implies that stress may interfere with important postpartum neuronal adaptations. Thus, 3hrs maternal separation, in the first two weeks after birth, may modify the degree and intensity of maternal care which are crucial for the normal brain development of offspring. Support: Regione Sardegna GRANT CRP -60921; Fondazione Banco di Sardegna Grant 2014.1993.

53. **The role of Mitogen and Stress activated protein Kinase 1 in response to environment enrichment throughout life.** Lorenzo Morè1, J. Simon Arthur2 and Bruno Frenguelli1. 1School of Life Sciences, The University of Warwick, U.K. 2College of Life Sciences, Sir James Black Centre, University of Dundee, U.K. Rodents reared in an enriched environment (EE) have been reported to show enhanced learning and memory, greater resilience to stressful situations, higher resistance to the addictive effects of drugs of abuse and improved recovery in both acquired and neurodegenerative brain injury. As such, considerable interest has arisen in the molecular mechanisms by which EE affects neuronal structure, synaptic function and cognition. We have previously shown that mice lacking the kinase activity of mitogen and stress activated kinase 1 (MSK1) did not display the enhancement of hippocampal synaptic transmission observed in wild-type (WT) mice after EE and showed a blunted increase in spine density. We concluded that MSK1 may transduce some of the positive effects of EE into lasting structural and functional neuronal changes. This suggestion is made plausible given that 1) MSK1 is downstream of BDNF-activated TrkB receptors and 2) MSK1 has the ability to regulate gene expression via the phosphorylation of both CREB at S133 and histone H3 at S10. A number of these processes have been implicated in mediating the positive effects of EE. The present work investigated the extent to which EE improved hippocampus-dependent spatial reference and working memory and cognitive flexibility in an MSK1-dependent manner during an early stage of life, i.e. from birth to 2.5-4 months of age, during a mid-stage of life, i.e. from 6 to 8.5-10.5 months of age and during an old stage of life, i.e. from 18 to 20.5-22.5 months of age. Our data show that the kinase activity of MSK1 is differently required during life for the full expression of the cognition-enhancing effects of EE. Generally MSK1 kinase-dead mice showed less improvement in hippocampus-dependent spatial reference memory and reversal learning tasks in the water-maze, and made fewer correct alternations during a spontaneous alternation task for spatial working memory. Anxiety and locomotion were not affected in a MSK1 dependent manner at any stage of life while reaction to novelty was differently affected in MSK1 and Wild-Type mice throughout life. These data suggest that MSK1 is necessary for the full conversion of positive environmental stimulation into the enhancement of cognition in early life and to provide a “cognitive reserve” in old animals. The present work was funded by the BBSRC and WPH.

54. **Does aberrant hippocampal neurogenesis affect rat’s behavior in different behavioral tests?** Ana Paula Ramos Costaa, Brunno Rocha Levoneb, Vagner Fagnani Linartevichia, FelipeVanza, Claudia Ailinne Vera Boutaudf, Camila Mariel Quiñones Valenzuelae, Cilene Lino de Oliveiraa,d,Thimoty G. Dinanb,c, Olivia O´learyb,c John F. Cryanb,c, Thereza Christina Monteiro de Limaa. a- Department of Pharmacology – Universidade Federal de Santa Catarina – Brazil, b- Department of Anatomy and Neuroscience – University College Cork – Ireland, c- APC Microbiome Institute – University College Cork, d- Department of Physiology – Universidade Federal de Santa Catarina – Brazil, e- Medicine Student from Universidad Nacional Andrés Bello – Chile, f- Medicine Student from Universidad Mayor Temuco – Chile. Adult hippocampal (HIP) neurogenesis (NG) has been related to learning, spatial memory, fear, antidepressant treatment (AD) and anxiety disorders. Several studies suggest that chronic stress can reduce adult HIP NG, while chronic AD treatment, physical exercises and environmental enrichment can increase the NG ratio. Recently, our research group showed that rats treated with a single injection of an

anxiogenic dose of pilocarpine (PIL) - a non-selective muscarinic receptor agonist – present an increase in defensive behavior (in the elevated plus maze and open field tests) and increased serum corticosterone levels that lasts from 24 h up to 30 days after the single injection. Moreover, the PIL treatment was able to increase NG in the HIP granular cell layer and hilus 30 days after PIL injection. Our hypothesis is that the aberrant NG can underlie the long-term behavioral changes after the PIL injection. Thus, to better understand the influence of this aberrant NG, we tested the PIL-treated animals on tasks partially dependent on NG in rats such as the novelty suppressed feeding test (NSF) and fear conditioning test (FCT). For the NSF we have used a modified protocol that does not involve food deprivation since we offered a palatable food portion to the animals in the central zone of the open field test. 24 hours after the injection, control and treated rats did not eat the food during the test, but all of them ate the entire amount when offered immediately after the test in their home cage. The same group of animals was retested 30 days after the treatment, and the treatment still not changing the performance of rats in this test, showing that the NG that occurs it is not enough to induce the feeding in the NSF. Other 2 groups of control and treated rats, were submitted to FCT (one 0,7mA foot shock for 3 sec) 24 h or 30 days after treatment. Similarly, the PIL-treated animals did not experience fear in a different way from control animals, 24 h or 30 days after the treatment. These results suggests that the behavioral changes caused by the single injection of PIL are restricted to unconditioned tasks that involves HIP circuitry, since we did not observed behavioral differences in conditioned responses. In the present model, increased NG apparently does not lead to a positive behavioral output. As a further matter, these findings will help to a better understanding of the involvement of cholinergic system in the HIP circuitry in emotional responses. Financial support was provided by SFI, CNPq, CAPES and APC. The agencies had no further role in the study design; in the collection,analysis and data interpretation. The protocols were conducted in strict adherence to the local Committee on Animal Care and Use.

55. **Adult hippocampal neurogenesis affects motivation to obtain sucrose, but not food, reward in operant tasks.** Rose-Marie Karlsson1, Alice S Wang1, Anup Sonti1 and Heather Cameron1. 1Section on Neuroplasticity, National Institute of Mental Health, National Institute of Health, Bethesda, MD, USA. Inability to experience pleasure in normally rewarding acts, anhedonia, is characteristic of many psychiatric disorders, including major depression, but is poorly understood. Our laboratory has previously shown that mice lacking neurogenesis exhibit a depression-like phenotype, including decreased sucrose preference, a standard measure for studying anhedonia in rodents. The aim of the present study was to further investigate the role of adult hippocampal neurogenesis in motivation to obtain novel rewards in both mice and rats. We inhibited adult neurogenesis using valganciclovir in transgenic mice and rats that express herpes simplex virus thymidine kinase (TK) in neural stem cells. We investigated the effect of this inhibition on instrumental learning, willingness to work and use of reward value representations, using chocolate flavored sucrose tablets or regular food tablets. TK and wild-type (WT) littermate controls showed similar acquisition of lever press and reward-paired cue association, suggesting normal associative learning. However, when switched to an exponentially progressive ratio (PR) task, both mice and rats lacking adult hippocampal neurogenesis showed significantly reduced lever responding compared to their WT controls when working for sucrose rewards. When working for food tablets, there was no difference between WT and TK animals. Similarly, when rats where tested on an effort-based task in which they could either press the reward-paired lever for a reward or consume the regular diet chow, available in the operant chamber, TK rats showed a significantly reduced effort to work for sucrose, but not for the food, tablets. This suggests that TK animals have a decreased motivation to expend effort for sucrose but normal motivation to obtain a novel food reward. The decreased motivation to earn sucrose was not due to the sensitivity to the value of the rewards, as TK mice and rats showed similar outcome devaluation. When given the opportunity to freely choose between sucrose and food rewards, there was a 5-fold preference for the food over the sucrose. Taken together, this suggests that new neurons affect behavior when motivation is relatively low. This is the first study to demonstrate that rodents lacking adult hippocampal neurogenesis have decreased motivation to work for a sucrose reward in effort-based tasks, consistent with the anhedonic phenotype seen in the sucrose preference test.

56. **Effect of venlafaxine and chronic unpredictable stress on behavior and hippocampal neurogenesis of rat dams.** Melicherčíková, K.1,2, Császár, E.1,2, Ujhazy, E.1, Mach, M.1, Dubovický, M.1. 1Institute of Experimental Pharmacology and Toxicology, Slovak Academy of Sciences, Bratislava, Slovakia. 2 Department of Pharmacology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia. Epidemiological studies strongly support the theory that stressful life events play an important role in the etiology of depression. The mechanism of chronic stress induced depression involves a number of systems. Chronic stress represents a serious health issue especially during pregnancy and lactation. In this sensitive period, stress can lead to changes in emotional and cognitive behavior both of the mothers and the offspring. It is thus necessary to properly manage stress events during gestation. Venlafaxine belongs to the serotonin and noradrenaline re-uptake inhibitor group. It is used for the treatment of depression, anxiety disorders and other mood disorders. During pregnancy, however, the use of venlafaxine is questionable due to the lack of experimental and clinical studies. Therefore the aim of this study was to evaluate the effect of chronic unpredictable stress and/or venlafaxine treatment on maternal behavior of dams as well as on emotional behavior of the females after the weaning period. Female Wistar rats were subjected to 2-week chronic unpredictable stress induced by random stressors and treated with venlafaxine orally at a dose of 5 mg/kg twice a day. Maternal behavior was evaluated within 5-min observations twice a day. Mothers were also tested in the open field 8 weeks after chronic unpredictable stress procedure in a single 15-min session. Immunohistochemistry essay using DCX staining was performed on brain sections of these animals. Results of the present study showed altered maternal and emotional behavior of the dams. Cognitive behavior of the females was not affected, yet stressed dams showed lower level of hippocampal neurogenesis, while venlafaxine treatment reversed this condition. These results suggest that stress and antidepressant therapy can have significant impact on neurobehavioral outcomes in rat dams. ACKNOWLEDGMENT VEGA 2/0168/15.

57. **Socio-sexual behaviors in ovariectomized rats housed in a seminatural environment and treated with the estrogen receptor α agonist propylpyrazoletriol (PPT) or the estrogen receptor β agonist diarylpropionitrile (DPN).** Olivia Le Moëne1, Anders Ågmo1. 1University of Tromso. The present study focused on the differential role of estrogen receptors (ER) α and β on socio-sexual interactions among rats. Ten groups of 7 rats (4 females and 3 males) were housed for 8 days in a semi-natural environment (SNE) consisting of a large open area and an adjacent burrow system. Females were ovariectomized about 2 weeks prior to the experiment and they, together with the intact males, were introduced into the SNE on day 0. On day 5, each female was given a different treatment: Control females, peanut oil, 1 ml/kg; estradiol females, 18 μg/kg 17β-estradiol benzoate; females α, 10 mg/kg propylpyrazoletriol (PPT); females β, 10 mg/kg diarylpropionitrile (DPN). On day 6, agonist treatment was repeated for females α and females β whereas the other females received peanut oil. On day 7, all females received 1 mg/rat of progesterone. The rats were observed for 45 minutes, beginning four hours after the injection of progesterone. The frequency and/or duration of all socio-sexual interactions were recorded. All females spent a substantial proportion of their time sleeping (41.8±4.7%), regardless of the treatment received. However, while all females slept more often alone than with other rats, females α slept more often with other females than alone or with male rats. The importance of this observation is somewhat unclear. When active, the estradiol females were more pursued and more sniffed by the males than control females and females β. The females α were intermediate. There were no other meaningful differences in social interactions between the different treatments. The lordosis quotient in estradiol females and in females α was close to 1 in both groups, and 0 in control and estradiol β females. These data show that estradiol or the ERα agonist PPT enhance female attractivity to the males. The fact that the females treated with the ERβ agonist DPN were not different from females given oil show that the ERβ does not contribute to female attractivity. Likewise, estradiol and PPT induced full receptivity in the females, whereas DPN had no effect. This latter observation coincides with a large amount of earlier data. It appears, then, that only the ERα is involved in the regulation of socio-sexual behaviors in the adult female.

58. **How many synapses does a single microglia monitor in the stratum radiatum of CA1?** Krejčova, LV1; Bento-Torres, J1; Guedes, RCA2; Oliveira, MA1; Perry, VH3; Picanço-Diniz CW1. 1Laboratório de Investigações em Neurodegeneração e Infecção, Hospital João de Barros Barreto, Instituto de Ciências Biológicas, Universidade Federal do Pará, CEP 66.073-005, Belém, Pará, Brasil. 2Laboratório de Fisiologia da Nutrição Naíde Teodósio, Departamento de Nutrição, Universidade Federal. 3 Centre for Biological Sciences, University of Southampton, Southampton, UK. There have been significant efforts to investigate the contribution of microglia in surveying their local environment in the brain parenchyma, and recently the focus has been on their role in surveying and monitoring synaptic health. We set out to estimate how many synapses fall within the territory of a single microglia cell to understand just how many synapses a single microglia may survey. The number of synapses/mm3 of neuropil in the stratum radiatum of rat has been estimated (Bartol et al 2015 , eLife. 2015; 4: e10778), thus we decided to measure the volume of tissue covered on average by a single microglia measuring the volume of 110 three-dimensionally reconstructed microglia. Five adult Wistar rats (4 months old), raised in standard laboratory conditions, were sacrificed and their brains were processed for selective microglia/macrophage immunolabeling with anti-IBA-1 antibodies. Microglial cells on the stratum radiatum of CA1 were randomly/systematically chosen and three-dimensionally reconstructed using NeuroLucida software. Bartol and colleagues counted all synapses in a small block of tissue of 6x6x5 µm3 of the stratum radiatum neuropil and found 449 synapses inside this volume of which 236 presynaptic boutons were fully contained in the volume. Considering the proposed spatial arrangement of theoretical territory surveyed by a single microglial cell (Jinno et al, 2007, GLIA 55:1334–1347), we used Sholl analysis to estimate the critical radius of the microglia and calculated that the volume of a single microglia was 310.18 x 10-6 mm3 with the equivalent circle radius of 42,1µm. Thus, correcting the volume density for shrinkage of 25% we estimated a total between 174,168 and 331,597 synapses inside a single microglial territory. We suggest that this number of synapses imposes a rather demanding role for the microglia to monitor every single synapse on its territory. However, the frequency of microglial contact with synapses, the number of synapses surveyed by a single process, the contact time per synapse and the mechanisms underlying these processes are still poorly understood.

59. **Androgen receptor overexpression leads to deficits in fear-conditioning in male mice.** FiryalRamzan1,2 , AmberAzam3 , AshleyMonks1,2,3 , IvaZovkic1,3. 1Department of Psychology, University of Toronto at Mississauga, 2Neuroscience, 3Cell and Systems Biology, University of Toronto. 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. There is also evidence that 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 males and females of both groups with their wild-type (WT) conspecifics. Behaviourally, we see that global AR overexpression leads to deficits in fear memory in male but not in female mice, suggesting that effects of AR overexpression are mediated by circulating testosterone. Consistent with this hypothesis, gonadectomy had no effect on females, but eliminated group differences between AR-overexpressing and WT males, implicating testosterone as a negative regulator of fear memory. These results suggest a role of AR in modulating fear conditioning memory. 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.

60. **Using circuit-directed behavioral induction of immediate early genes as a biomarker for circuit integrity during recovery of brain injury.** Theresa Currier Thomas1-3, Aida Khodadad2,4, P. David Adelson1,2, Jonathan Lifshitz1-3, 1BARROW Neurological Institute at Phoenix Children's Hospital-

Phoenix, AZ. 2Child Health, University of Arizona College of Medicine – Phoenix, AZ. 3Phoenix VA Healthcare System- Phoenix, AZ. 4Neuroscience, University of Strasbourg, France. After experimental diffuse TBI, there is behavioral, structural and functional evidence that injured circuits are disrupted, then dismantled and eventually reorganized. A molecular biomarker of behavior-based circuit activation could elucidate disruption and concurrent impact of rehabilitative intervention on circuit integrity. Immediate early genes (IEG) are tightly coupled to activation in behavioral paradigms and could serve as a molecular marker of circuit activity to reveal the impact of behavior-based rehabilitation after TBI. In male SD rats (~325g), we have identified ARC as a potential IEG target, identified ARC's gene and protein expression time course after circuit stimulation and confirmed that our rehabilitation paradigm activates the targeted circuit. Ongoing experiments are assessing injury-induced changes in circuit activation and evaluating the impact of an early onset rehabilitation paradigm over time. Successful completion of these experiments would provide a foundation for assessing the structural and functional impact of type, timing and onset of physical rehabilitation after TBI. Supported, in part, by NIH R03 NS077098, NIH R01 NS065052 and PCH Mission Support.

61. **Using circuit-directed behavioral induction of immediate early genes as a biomarker for circuit integrity during recovery of brain injury.** Theresa Currier Thomas1-3, Aida Khodadad2,4, P. David Adelson1,2, Jonathan Lifshitz1-3, 1BARROW Neurological Institute at Phoenix Children's Hospital-Phoenix, AZ 2Child Health, University of Arizona College of Medicine – Phoenix, AZ 3Phoenix VA Healthcare System- Phoenix, AZ 4Neuroscience, University of Strasbourg, France After experimental diffuse TBI, there is behavioral, structural and functional evidence that injured circuits are disrupted, then dismantled and eventually reorganized. A molecular biomarker of behavior-based circuit activation could elucidate disruption and concurrent impact of rehabilitative intervention on circuit integrity. Immediate early genes (IEG) are tightly coupled to activation in behavioral paradigms and could serve as a molecular marker of circuit activity to reveal the impact of behavior-based rehabilitation after TBI. In male SD rats (~325g), we have identified ARC as a potential IEG target, identified ARC's gene and protein expression time course after circuit stimulation and confirmed that our rehabilitation paradigm activates the targeted circuit. Ongoing experiments are assessing injury-induced changes in circuit activation and evaluating the impact of an early onset rehabilitation paradigm over time. Successful completion of these experiments would provide a foundation for assessing the structural and functional impact of type, timing and onset of physical rehabilitation after TBI. Supported, in part, by NIH R03 NS077098, NIH R01 NS065052 and PCH Mission Support.

62. **Investigation of sucrose preference in large home cage with environmental enrichment.** Büki A., Kekesi G., Benedek G., Horvath G. Dept. Physiol., Fac. Med., Univ. Szeged, Szeged, Hungary. Introduction: It is well known that a large home cage with environmental enrichment enhances the learning capability of the animals. The goal of this study was to reveal the potential alterations in sucrose preference in a new substrain showing disturbances related to schizophrenia investigated in a large home cage with running wheel. Methods: Two experimental groups of male Wistar rats were studied (n=6-6 rats/group): naive rats without any treatment and the 23-24rd generations of selectively bred animals with social isolation and ketamine treatment at the age of 4-7 weeks followed by resocialization. The tail-flick, the startle reflex and the simplified holeboard tests were performed at the age of two months to compare the pain sensitivity, the acoustic startle reaction and the learning capabilities of the two groups. At the age of 3 month, rats were housed individually in a 3-storeyed large cage (57x29x55 cm) with two bottles; one was filled with tap water on the second floor and the other with sucrose solution (2 %) on the third floor for four days. Two series of experiments were performed: (1) the food amount was the double on the third as on the second floor, (2) the amount of the food was equal on both places. Fluid and food consumptions were measured daily and referred to body weight, and a preference ratio was calculated for sucrose/total fluid intake. Results: The new substrain showed decreased pain sensitivity, higher degree of startle reaction, reduced exploratory activity, disturbed cognitive performance and lower body weight. There were no significant differences in total fluid and food consumptions between the groups. The food consumption depended on series, thus the animals ate more where the supply was higher, but the groups

did not differ in this respect. The food supply did not influence the total fluid intake. Sucrose preference was significantly lower in the new substrain at the first day, but the preference ratio increased by time in these animals. Conclusion: Our results showed that animals with several cognitive and behavioral abnormalities have no anhedonia in sucrose preference test applied in a large home cage with environmental enrichment, but their learning capability was lower in this test too, suggesting that this model is not sensitive to simulate this symptom of schizophrenia. This work was supported by OTKA (K83810), TÁMOP-4.2.2.B-15/1/KONV-2015-0006.

63. **AMBITUS system, a rectangular corridor for the investigation of cognitive function.** Horvath G., Liszli P., Kekesi G., Büki A., Benedek G. Dept. Physiol., Fac. Med., Univ. Szeged, Szeged, Hungary. The rodent tasks with food rewards are useful approaches to describe memory functions of animals; therefore, it is important to establish reliable and automated methods with high throughput to evaluate learning capability. It is well-known that in contrast to a hole-board with open field, rats prefer the narrow tunnels. Based on this assumption, a new instrument named AMBITUS system ("to go round") was developed, which is a rectangular corridor with side-boxes. The advantages of this new system include the shape (corridor without open field) and the possibility for separately analysis of each box or in the chain of inner and outer boxes ensures the investigation of spatial and reversal learning capabilities applying different protocols. Experiments were performed to validate this instrument for task acquirement and learning flexibility. Methods: The rectangular corridor was constructed with 8-8 side-boxes containing food rewards along the inner and outer sides of each wall. Photocells at each boxes recorded the nose-poking activity, while the eating parameters were obtained offline from video records. 14 male adult Wistar rats were exposed to two types of tasks repeatedly for 5 minutes; Task-1: all of the side-boxes were baited, and Task-2: only the inside boxes were baited. The number, latency and frequency of ambulations, the number of eaten food rewards and the time required to collect all of the rice were detected. Results: Most of the animals acquired the Task-1 and their performance improved gradually during 8 trials. The introduction of the Task-2 caused preference of the inner side, thus, a learning capability in the avoidance of unbaited boxes could be seen during the trials of Task-2, resulting in the rats' moving less redundantly over trials. The comparison of manual and automated scoring of the ambulatory activity showed close correlation. Discussion: Healthy animals can perform the simple tasks in the rectangular corridor after few repetitions; furthermore the AMBITUS system might be appropriate to detect cognitive flexibility. The AMBITUS system is an efficient and reliable way for assessment the activity and learning capacity of rats. This work was supported by OTKA (K83810), TÁMOP-4.2.2.B-15/1/KONV-2015-0006.

Saturday, June 11

8:00-10:00 ***Individual vulnerability to addiction: Dissection of behavior, neural circuits, cellular and molecular mechanisms.*** Chair: Gabor Egervari; Co-Chair: Yasmin Hurd.

Inter-individual differences in cocaine and heroin addiction in the rat: Behavioural and neurobiological mechanisms. Belin, D., University of Cambridge, UK. Preclinical models of drug addiction have been developed for cocaine over the last decade. They have contributed to disentangle the environmental, behavioural and neurobiological factors contributing to the propensity to use cocaine from those contributing to the vulnerability to switch from controlled to compulsive cocaine use. However, there were, until very recently, no preclinical models of compulsive heroin seeking behaviour. While presenting an overview of the factors contributing to cocaine addiction in the rat, we will also describe a preclinical model of addiction to heroin and the psychological and neurobiological mechanisms contributing to individual differences to compulsive heroin seeking behaviour.

When the brakes fail: mPFC plasticity mechanisms in drug seeking. Taco J. De Vries. Neuroscience Campus Amsterdam, Dept of Anatomy and Neurosciences, VU University medical center, and CNCR, Faculty of Earth and Life Sciences, VU University, Amsterdam, The Netherlands. I will give an update of our studies on cellular mechanisms of drug relapse in rat models of i.v. heroin and nicotine self-administration. Our data indicate that cue-induced relapse to heroin and nicotine seeking is mediated by distinct synaptic plasticity mechanisms and molecular adaptations (as assessed by neuroproteomic methods) in subregions of the mPFC. Recent analysis (using optogenetic interventions) of the role of mPFC glutamatergic neurons in cue-evoked nicotine seeking will also be presented. Finally, I will discuss a recent behavioural intervention aimed at reducing nicotine cue-reactivity by working memory interference.

Contribution of genetic and environmental factors in the regulation of stress mechanisms and individual vulnerability to drugs of abuse. Roberto Ciccocioppo1, Esi Domi1, Giulia Scuppa1, Gloria Brunori1, Quienwei Shen1, Massimo Ubaldi1. 1University of Camerino, School of Pharmacy, Pharmacology Unit, Camerino, Italy. Addiction is an etiologically and clinically heterogeneous disorder in which uncontrollable urge to use the drug represent a core symptom. Exposure to psychoactive agents is a necessary precondition. However, environmental and heritability factors can play a dramatic role in controlling individual vulnerability to developing addiction. Data will be presented showing that genetically determined predisposition to high anxiety and negative mood states are associated with innate propensity to develop addictive-like behaviors. Specifically, studies in genetically selected Marchigian Sardinian alcohol-preferring (msP) rats, an animal line selected for excessive EtOH drinking, reveal that comorbidity between excessive drinking and negative affect is linked to polymorphism of the Corticotropin-Releasing Factor 1 Receptor (CRF1R) promoter, leading to enhanced CRF1R density in the limbic regions. MsP rats are also characterized by innate overexpression of the opioid nociceptin/orphanin FQ (N/OFQ) system in the same brain regions. On the other hand, genetic deletion of the N/OFQ receptor (NOP) Wistar rats, confers resilience to develop addictive-like behaviors triggered by cocaine, heroin and alcohol. Notably, a history of EtOH intoxication in outbred Wistars lead to enhanced expression of CRF1R and N/OFQ-NOP receptor systems which may contribute to their excessive alcohol consumption. Finally we found that voluntary alcohol drinking is capable to reverse the overexpression of CRFR1 and NOP systems and attenuates hyperanxiety and depression-like behaviors. A tempting hypothesis is that drug intake is motivated by self-medication mechanisms, and their consumption is an attempts to self-medicate from innate predetermined or environmentally evoked negative affect. Work supported by grant (NIAAA: RO1 AA017447, and RO1 AA014351).

Prodynorphin genetic polymorphisms and ventral striatonigral pathway activity contribute to individual differences in novelty seeking and positive reward traits. Gabor Egervari1,2, Didier Jutras-Aswad1, Joseph Landry1,2, Michael L Miller1,2, Sarah Ann Anderson1,2, Michael Michaelides1,2, Michelle M Jacobs1,2, Cyril Peter1,2, Georgia Yiannoulos1, Xun Liu1, Yasmin L Hurd1,2. 1 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029, USA. 2 Department of Neuroscience, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029, USA. Genetic factors impact behavioral traits relevant to numerous psychiatric disorders and risk-taking behaviors, and different lines of evidence have indicated that discrete neurobiological systems contribute to such individual differences. This presentation will explore the relationship of genetic variants associated with neural circuits implicated in reward and novelty-seeking traits. Specifically, we focus on the prodynorphin (PDYN) gene that is enriched in the ventral striatonigral/striatomesencephalic pathway, a key neuronal circuit implicated in positive 'Go' behavioral choice and action. Our multidisciplinary approach identified a single nucleotide polymorphism (SNP), rs2235749 that modifies striatal PDYN expression through altering the binding of miR-365, a microRNA that targets the PDYN 3'-untranslated region. The SNP is significantly associated with PDYN mRNA expression particularly in the nucleus accumbens shell (NAcSh) as well as to novelty- and reward-related behavioral traits in humans and translational animal models. We provide evidence that the Pdyn-miR365 interaction in the NAcSh directly influences novelty seeking exploratory behavior and facilitates the self-administration of natural rewards. Overall, this translational study suggests that genetically determined

miR-365-mediated epigenetic regulation of PDYN expression in mesolimbic striatonigral/striatomesencephalic circuits contributes to novelty seeking and positive reinforcement traits. The findings will be discussed in relation to individual vulnerability to addiction and related disorders. This work was funded by NIH DA15446.

8:00-10:00 ***Integrated neuromodulatory control of arousal and complex behaviours: Focus on dual transmitter systems and networks.*** Chair: Sherie Ma; Co-Chair: William Wisden.

Histamine and GABA co-transmission promote arousal. Wisden, William1; Yu, Xiao1; Ye, Zhiwen1; Houston, Cat1; Brickley, Stephen G1; Franks, Nicholas P1. 1Dept of Life Sciences, Imperial College London, UK. Histamine neurons in the posterior hypothalamus project widely in the brain. It has been known for many years that these neurons also contain gamma-amino butyric acid (GABA). In fact, GABA was discovered in these cells before the discovery that they contained histamine. We have been studying the function of this GABA in histamine neurons by deleting the vesicular GABA transporter gene from histaminergic cells. This produces mice which are hyperactive during the “lights on” period. We have shown that in the neocortex and striatum histaminergic neurons co-release GABA to produce a special type of extrasynaptic (tonic) inhibition i.e. volume transmission. However, in the ventral lateral preoptic hypothalamic nucleus, which is active during sleep, there are pure histaminergic afferents. It is likely that there are subtypes of histaminergic cells, some of which that contain GABA, regulating different aspects of behavior. The co-released GABA may act to sharpen cognition or act as a brake on too much histamine release. Too much histamine release seems to promote a mania-like behavior.

Interactions of glutamate/orexin and GABA/MCH systems with arousal. networks. Christopher S. Leonard. New York Medical College, Valhalla, New York USA. Orexin/hypocretin and MCH peptide synthesizing neurons are intermingled in the lateral hypothalamus and have many similar projections to brain structures implicated in the regulation of sleep-wake states, motivation and metabolism, including regions rich in monoaminergic and cholinergic neurons. Knockout studies of each of these peptides, suggest they play critical but complementary roles in modulating behavior. For example, orexin ligand knockout mice are susceptible to obesity and have a narcolepsy phenotype, showing fragmented sleep/waking states with cataplexy, similar to human narcoleptics, whose orexin neurons degenerate. In contrast, MCH knockouts are lean and show reduced non-REM sleep and greater waking time than wild type littermates. Recent optogenetic and chemogenetic studies strongly support these roles but the critical sites of peptide action and the relative importance of the co-released small molecule transmitters are incompletely understood. Moreover, while orexin and MCH are respectively known as slow “excitatory” and “inhibitory” peptides, their pre-and post-synaptic actions can be complex. My presentation will review these peptide systems and discuss emerging evidence that orexin and MCH play modulatory roles that help “tune” the post-synaptic properties of their target neurons for integrating state-control signals carried by convergent pathways.

Central cholinergic neurons are rapidly recruited by reinforcement feedback. Balázs Hangya1,2, Sachin P. Ranade1, Maja Lorenc1, Adam Kepecs1. 1Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 11724, United States. 2Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, H-1083, Hungary. Basal forebrain cholinergic neurons constitute a major neuromodulatory system implicated in normal cognition and neurodegenerative dementias. Cholinergic projections densely innervate the cortex, releasing acetylcholine to regulate arousal, attention and learning. However, their precise behavioral function is poorly understood because identified cholinergic neurons have never been recorded during behavior. To determine which aspects of cognition their activity might support we recorded cholinergic neurons using optogenetic identification in mice performing an auditory detection task requiring sustained attention. We found that a non-cholinergic basal forebrain

population, but not cholinergic neurons, were correlated with trial-to-trial measures of attention. Surprisingly, cholinergic neurons responded phasically to primary reward and punishment with remarkable speed and precision (18±3 ms), unexpected for a neuromodulatory system. Responses to reward were scaled by reinforcement surprise, raising the possibility that the cholinergic system also conveys cognitive information. These results suggest that cholinergic neurons form a rapid, reliable and temporally precise signalling route for reinforcement feedback that can mediate fast cortical activation and plasticity.

Nucleus incertus, GABA and relaxin-3: an emerging modulatory role in arousal, stress and memory. Sherie Ma1,2, Giancarlo Allocca1,2, Emma EKE Ong-Palsson1,2; Caitlin E. Singleton1,2; Spencer J Williams3; Ross AD Bathgate1,2,4; Andrew L. Gundlach1,2,5. 1The Florey Institute of Neuroscience and Mental Health; and 2Florey Department of Neuroscience and Mental Health, 3School of Chemistry and Bio21 Molecular Science and Biotechnology Institute, 4Department of Biochemistry and Molecular Biology, 5Department of Anatomy and Neuroscience, The University of Melbourne, Victoria 3010, Australia. The nucleus incertus (NI) of the pontine periventricular grey consists of GABAergic neurons with long-range ascending projections to forebrain. Efferent and afferent connections implicate the NI in processes of 'behavioural planning, habenular function, hippocampal/cortical activity in attention/memory, and in oculomotor control'. The NI is a site of corticotropin-releasing factor (CRF) and orexin action, and forms a neural circuit positioned to modulate arousal and stress responses and the de/synchronization of hippocampal oscillatory theta (4-12 Hz) rhythm, prominent in the electroencephalograph (EEG) during exploration and memory processes. Theta rhythm underlies goal-oriented behaviour and cognition, and is a neurophysiological signature of REM sleep. The NI is also a primary site for neurons expressing the neuropeptide, relaxin-3, which can modulate septohippocampal activity and theta rhythm, and are associated with spatial working memory in the rat. However, NI function in awake, behaving animals remains unclear. Therefore, we used a pharmacogenetic approach (i.e. designer receptors exclusively activated by designer drugs, DREADDs) to modulate NI activity in freely-moving rats and assessed the behavioural and physiological consequences. An adeno-associated viral vector was used to transduce excitatory hM3Dq or inhibitory hM4Di into NI neurons of adult male rats. For behavioural and EEG recordings, DREADDs were activated by the designer ligand, clozapine-N-oxide (CNO). In hM3Dq-expressing rats, CNO activation of NI networks produced long-lasting theta activity, associated with increased locomotor activity and wakefulness, suggesting effects related to increased arousal and impairment of habituation and rest. Consistent with inactivation of the NI, hM4Di-expressing rats exhibited impaired spatial memory performance in the Morris water maze and Y maze. Current data suggest NI activity regulates behavioural state and I will review our findings on this emerging, integrative neural network associated with broad GABA/neuropeptide release, and its therapeutic potential.

10:30 **Keynote Speaker. Urs Meyer**, Institute of Pharmacology and Toxicology, University of Zurich, Switzerland. Developmental Neuroinflammation and Long-Term Brain Pathology: From Models and Mechanisms to Transgenerational Effects.

Developmental neuroinflammation and long-term brain pathology: From models and mechanisms to transgenerational effects. Meyer, Urs1. 1Institute of Pharmacology and Toxicology, University of Zurich, Vetsuisse Faculty, Winterthurerstrasse 260, 8057 Zurich, Switzerland. Prenatal exposure to infection is increasingly recognized to play an important etiological role in neuropsychiatric and neurological disorders with neurodevelopmental components, including schizophrenia, autism, bipolar disorder, and mental retardation. The adverse effects induced by prenatal infection may reflect an early entry into a deviant neurodevelopmental route, but the specificity of subsequent disease or symptoms is likely to be influenced by the genetic and environmental context in which the prenatal infectious process occurs. The epidemiological link between prenatal infection and increased risk of neurodevelopmental disorders also receives strong support from experimental work in animal models. These models are based on maternal

gestational exposure to specific infectious agents such as influenza virus or immune activating agents such as the bacterial endotoxin lipopolysaccharide (LPS) or the viral mimic poly(I:C). Converging evidence form these models suggests that prenatal immune activation can negatively affect early fetal brain development and change the offspring's neurodevelopmental trajectories, which in turn can lead to the emergence of behavioral and cognitive disturbances in later life. Modeling the human epidemiological association between prenatal infection and increased risk of neurodevelopmental disorders in animals has also greatly advanced our understanding of the underlying mechanisms. According to the prevailing view, cytokine-associated inflammatory events, together with downstream pathophysiological effects such as oxidative stress and (temporary) macronutrient and micronutrient deficiency, seem critical in mediating the post-acute effects of maternal infection on the fetal system. Recent findings have further implicated epigenetic processes as possible molecular mechanisms translating the negative effects of prenatal immune activation on the offspring. Not only does prenatal immune activation cause long-lasting epigenetic modifications such as altered DNA methylation and miRNA expression, but it also causes a transgenerational transmission of behavioral and neuronal abnormalities without additional immune exposures. Hence, prenatal infection and associated developmental neuroinflammation may have a pathological role in shaping neurodevelopmental disease risk across generations.

1:30-3:30 ***Exploring novel systems involved in the aetiology and potential treatment of anxiety disorders.*** Chair: David Slattery; Co-Chair: Clara Perani.

Assessing the role of oxytocin and neuropeptide S in anxiety-related behavior. Slattery, David; Jurek, Ben; Martinetz, Stefanie; Grund, Thomas; Neumann, Inga. Department of Behavioural and Molecular Neurobiology, University of Regensburg, Germany. Anxiety disorders are among the most common psychiatric illnesses, with a lifetime prevalence of approximately 30%. While a number of pharmacotherapies are available, the lack of truly novel-acting compounds has led to a focus on the development of non-GABAergic compounds. Neuropeptides represent such potential targets due to their distinct synthesis and release sites, and multiple behavioral functions. Two such neuropeptides are oxytocin and neuropeptide S (NPS). The former has been revealed as a profound anxiolytic and anti-stress factor of the brain, besides its many prosocial and reproductive effects. NPS has generated substantial interest due to its anxiolytic and fear-attenuating effects in rodents, while a corresponding receptor polymorphism associated with increased NPS receptor (NPSR1) surface expression and efficacy has been implicated in an increased risk of panic disorder in humans. Therefore, there is substantial scientific and medical interest in the potential therapeutic use of these neuropeptides for the treatment of psychopathologies associated with anxiety, fear, and social dysfunctions, such as generalized anxiety disorder, posttraumatic stress disorder, and social anxiety disorder. In this talk, I will discuss our recent findings revealing the regulatory capacity of OXT to fine-tune general and social anxiety-related behaviours and those suggesting that alterations in the NPS system, conserved across rodents and humans, contribute to innate anxiety and fear.

Marijuana as Medicine: Targeting cannabinoid-modulating circuits to treat anxiety. The mission of the Laboratory of Behavioral and Genomic Neuroscience is to contribute to a deeper understanding of the causes of alcoholism and comorbid neuropsychiatric conditions such as mood and anxiety disorders. Our goal is to help identify new directions for the prevention and effective treatment of these devastating diseases. To this end, we are using models of chronic alcohol exposure and chronic stress to examine how these environmental insults reshape brain circuits to modify behavior, and why they do so in a manner that varies greatly from individual to individual as a function of genetics, sex and age. A major current focus of our work is how alcohol and stress affect the structure and function of circuits interconnecting the prefrontal cortex with limbic and dorsal striatal regions that are critical for the regulation of emotion, cognition and executive control over drug-seeking. For more info:

http://niaaa.nih.gov/research/niaaa-intramural-program/niaaa-laboratories/laboratory-behavioral-and-genomic-neuroscience.

Stress exposure and High-Fat diet alter maternal anxiety-related behaviour and hypothalamus-pituitary-adrenal axis function. Perani CV1,2, Hillerer KH1,3, Neumann ID1, Slattery DA1. 1Department of Behavioural and Molecular Neurobiology, University of Regensburg, Regensburg, Germany. 2Department of Obstetrics and Fetal Medicine, Laboratory for Experimental Feto-Maternal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. 3Department of Obstetrics and Gynaecology, Perinatal Research Unit, Salzburger Landeskrankenhaus (SALK), Salzburg, Austria. Anxiety disorders are highly prevalent during pregnancy and the postpartum period despite the fact that these times are generally characterised by enhanced calmness / anxiolysis and reduced behavioural and hormonal response to stressful events. The alterations in anxiety and stress responsiveness are driven, at least in part, via adaptations in hypothalamus-pituitary-adrenal (HPA) axis function. Specifically, basal circulating glucocorticoids, the main HPA axis effectors, are elevated and stress-induced increases in glucocorticoids levels are reduced starting from mid-pregnancy in several species. Whilst factors increasing the risk for the development of anxiety peripartum including chronic stress and obesity were identified, the underlying mechanisms are largely unknown. Here, we hypothesised that stress and obesity act perturbing maternal HPA axis function. To test our hypothesis, we exposed pregnant rat to chronic stress or High-Fat diet and assessed the effects of these interventions on maternal and anxiety-related behaviour and on basal and stress-induced adrenocorticotropic hormone (ACTH) and corticosterone. Chronic stress exposure during pregnancy but not diet intervention affected maternal behaviour. Indeed, stressed dams performed active nursing more often compared with non–stressed mothers. Both stress and High-Fat diet intake altered anxiety-related behaviour. Specifically, stressed dams spent less time on the open arms of the elevated plus-maze compared with non-stress mothers and High-Fat diet prevented lactation-associated anxiolysis tested via the light-dark box test. These behavioural effects were accompanied by changes in circulating corticosterone. Both chronic stress and High-Fat diet blunted the lactation-associated basal increase in corticosterone without changes in ACTH. Corticosterone levels after 5 minutes forced swim were not affected; importantly, intravenous ACTH injection elicited higher corticosterone plasma levels in High-Fat compared with normal-fed dams. To conclude, we identified that chronic stress and High-Fat diet intake during pregnancy increased maternal care and anxiety-related behaviour and that these behavioural abnormalities were accompanied by altered maternal corticosterone levels without changes in ACTH in the rat. These findings suggest that HPA axis dysregulation, and particularly the adrenal gland, may represent key pathological features and potential site of treatment strategies of maternal anxiety disorders.

The Microbiota-Gut-Brain Axis As a Novel Strategy for Targeting Anxiety Disorders. Cryan, John F. University College Cork, Ireland. The concept of the gut influencing brain and behaviour has existed for almost two centuries. However, a new player has emerged in the past decade: the gut microbiota, which is now seen as a key regulator of the gut-brain axis. The gut is home to a diverse array of trillions of microbes which significantly to outnumber human cells. Advances in sequencing technologies show that the microbiota influences almost all aspects of human biology. Evidence of a crucial role for the microbiota in regulating stress-related changes in physiology, behaviour, and brain function has emerged mostly from animal studies. Mice that grow up devoid of a microbiome (in a germ-free environment) have an exaggerated hypothalamic-pituitary axis response to stress and altered anxiety-related behaviours. Converse findings have shown that stress (either early in life or in adulthood) changes microbiota composition. Moreover, the concept that bacteria were required for normal brain development has emerged and that the microbiota is regulates many key processes in the adult brain, such as

neurogenesis, blood brain barrier function and microglia activation. Thus, the ability to target the brain via the microbiome is viewed as a paradigm shift in neuroscience and psychiatry and has led to the concept of psychobiotics (bacteria with positive effects on mental health) being put forward. Animal studies again lead the way in showing that specific strains of bifidobacteria, lactobacilli, or bacteroides can have positive effects on the brain and behaviour. These studies are slowly being translated into research with healthy human volunteers. One immediate research goal is to elucidate the mechanisms underpinning the beneficial effects of specific bacterial strains in modulating anxiety behaviour. The role of microbiota composition as a susceptibility factor for various stressful insults, especially at key neurodevelopmental windows, is also emerging.

1:30-3:30 ***Developmental rodent models of behavioral dysfunction in neuropsychiatry: Disrupting the excitatory/inhibitory balance.*** Chair: Jared Young; Co-Chair: Susan Powell.

Rat model of prenatal malnutrition: prefrontal cortical dysfunction and neuropsychiatric implications. Jill A. McGaughy1 and Janina R. Galler2 1. University of New Hampshire. 5. The Chester M. Pierce, M. D., Division of Global Psychiatry, Massachusetts General Hospital and Department of Psychiatry, Harvard Medical School, Boston, MA 02120, United States Worldwide malnutrition is estimated to impact approximately 1 in 4 children. Studies of adults in China as well as the Netherlands have shown an increased prevalence of neuropsychiatric disorders in adults who were exposed to famine in utero or in early childhood. Convergent evidence from long-term studies of adults exposed to malnutrition in the first year of life in Barbados also show increases in the prevalence of neuropsychiatric disorders with specific impairments in attentional, and affective processing. Parents and teacher ratings of attention confirmed impairments in childhood and adolescence, that persisted into middle adulthood as measured by self-report. Insights related to the impact on the brain of prenatal protein malnutrition have been gained through the use of a rat model of this developmental insult. The offspring of rat dams assigned to receive either a low-protein (6% casein) or high protein (25% casein) diet prior to and throughout pregnancy are fostered to well-nourished dams. Adult rats have been tested in a series of studies aimed at assessing attention and determining the neurochemical, neuroanatomical and epigenetic changes in the prefrontal sub-regions that may underlie these disruptions in attentional processing. Over several studies, we have found that rats exposed to prenatal protein malnutrition (6/25) show cognitive rigidity in tests of attentional set shifting and distractibility when compared to control subjects (25/25) recapitulating attentional impairments found in the Barbados Nutrition Study. We have also found diet-related changes in prefrontal noradrenergic innervation of the region, monoaminergic neurochemistry, decreased metabolic activity and perturbations in KCNJ3 (GIRK1). These data support the hypotheses that that attentional impairments produced by malnutrition persist across the lifespan, and that these impairments arise from disruptions to the inhibitory/excitatory balance in the prefrontal cortices. Support NIH MH074811 (JRG) HD060986 (JRG).

Cognition, glutamate, and developmental vitamin D-deficiency in rodents. Thomas H. J. Burne. Queensland Brain Institute, The University of Queensland, Australia. Vitamin D deficiency is common in the adult population. Despite abundant sunlight, recent population-based studies indicate that 35% of Australians over 25 years of age have suboptimal levels of vitamin D (<50 nM). We have an ongoing program of research to examine the effects of hypovitaminosis D during pregnancy and in adulthood in animal models. The focus of my presentation will be on the mechanism by which vitamin D, a steroid hormone with diverse physiological roles, can influence brain function and behaviour. We have shown that gestational and adult vitamin D deficiency leads to alterations in both excitatory and inhibitory neurotransmitters in whole brain, as well as key enzymes involved with their synthesis. We also have data to show that there are subtle but persistent effects on behaviours with relevance to the positive symptoms of schizophrenia and altered cognitive function. This research has translatable implications for public health because vitamin D is a modifiable risk factor and vitamin D supplementation is safe and cheap and

could be addressed within the framework of recommendations for the consumption of other key nutrients. Funding acknowledged from the National Health and Medical Research Council of Australia.

Effects of perinatal and adolescent oxidative stress on inhibitory interneurons and behavior in mice. Susan Powell1,2; Asma Khan1,2, Loek A.W. de Jong1, Mary E. Kamenski1, Kerin K. Higa1, Jacinta D. Lucero3, Jared W. Young1,2, M. Margarita Behrens3. 1Dept of Psychiatry, University of California San Diego, La Jolla, CA; 2 Research Service, VA San Diego Healthcare System, San Diego, CA, 3 The Salk Institute for Biological Studies, La Jolla, CA. Decreased number of GABAergic neurons is a consistent finding in schizophrenia postmortem studies, where the subpopulation of parvalbumin-expressing (PV) fast-spiking inhibitory neurons is specifically affected. Deficits in cortical fast-spiking inhibitory systems may underlie the cognitive and emotional disturbances associated with many neuropsychiatric disorders. Environmental insults during the perinatal period or adolescence may be particularly detrimental to inhibitory circuits that have a protracted development. One likely effect of these environmental insults is to increase oxidative stress in the developing brain. Indeed, there is increasing evidence that redox dysregulation plays an important role in the development of schizophrenia and other neuropsychiatric disorders and that GABA interneurons are particularly susceptible to alterations in oxidative stress. For example, perinatal exposure of mice to the NMDA receptor antagonist ketamine (pNK) results in loss of PV+ immunoreactivity in the prelimbic cortex by increasing oxidative stress. Mice exposed to ketamine during the perinatal period also showed decreased social approach behavior and enhanced contextual and cued fear conditioning compared to saline-injected mice. Similarly, the adolescent period in mammals is a critical period of brain maturation and thus represents a time of susceptibility to environmental insult, e.g. psychosocial stress and/or drugs of abuse, which may cause lasting impairments in brain function and behavior and even precipitate symptoms in at risk individuals. To model adolescent neurochemical “stress” we exposed mice to the dopamine transporter inhibitor GBR12909 during adolescence and the resultant effect on locomotor behavior and probabilistic reversal learning as well as GABAergic interneurons and oxidative stress were measured. Mice exposed to GBR12909 showed increased activity in a novel environment and increased impulsivity as measured by premature responding in the probabilistic reversal learning task. Adolescent GBR12909-exposed mice also showed decreased parvalbumin (PV) immunoreactivity in the prefrontal cortex, which was accompanied by increased oxidative stress in PV+ neurons. These findings indicate that adolescent oxidative stress induced by a dopamine transporter inhibitor results in loss of PV in GABAergic interneurons and alterations in behavior in adulthood. Taken together these findings indicate that both the perinatal period and adolescence represent sensitive periods for redox dysregulation which impairs prefrontal inhibitory circuits and behavior. Supported by MH091407.

Reducing neuronal transcription factor Sp4 alters glutamatergic/NMDA receptor function and behaviors relevant to serious mental illness. Jared W. Young and Xianjin Zhou. Department of Psychiatry, University of California San Diego, La Jolla, USA, & Veteran’s Affairs, MIRECC, 3350 La Jolla Drive, La Jolla CA. Serious mental illness occurs in 25% of the general population, with most disorders being life-long and debilitating. The transcription factor Specificity Protein 4 (SP4) is important for neurodevelopment and is genetically associated with both schizophrenia and bipolar disorder. Reducing Sp4 expression in mice (hypomorphic) reproduces several characteristics of psychiatric disorders including behavioral and reduced NMDA receptor1 expression. We examined whether Sp4 hypomorphic mice would exhibit psychiatry-relevant deficits in cross-species tests. Sp4 hypomorphic and wildtype mice (n=17/11) were trained and tested in a variety of tasks including the 5-Choice Continuous Performance Test (cognitive control), probabilistic learning task (reward learning), and progressive ratio breakpoint (motivation). The effects of elevating glycine on these behaviors by inhibiting the glycine type-1 transporter (GlyT-1) were also examined. Hypomorphic mice exhibited reduced cognitive control, reduced motivation, and impaired reward learning. Neither motivational nor reward learning deficits of hypomorphic mice were attenuated by GlyT-1 treatment. Cognitive control deficits of these mice were however, attenuated by GlyT-1 inhibition ($p<0.05$), but impaired cognitive control in wildtype mice ($p<0.05$), as demonstrated by a genotype by drug interaction ($F(2,32)=4.9$, $p<0.05$). The impaired cognitive control and motivation/reward learning may arise from differing mechanisms. The GlyT-1

reversal of poor cognitive control provides support that personalized GlyT-1 inhibition may treat such deficits in neuropsychiatric patients with low SP4 levels and/or altered excitatory/inhibitory balance.

4:00-5:00 ***Function and neuroplasticity in the mesocorticolimbic system and alcohol dependence.*** Chair: Giovanni Biggio; Co-Chair: David M. Lovinger.

Synaptic Adaptations in the Dorsal Striatum and their Role in Alcohol-Related Habits. David M. Lovinger, Laboratory for Integrative Neuroscience, National Institute on Alcohol Abuse and Alcoholism, Bethesda, USA, 20892. Alcohol use is initially driven by the rewarding effects of the drug, but often progresses to stages where relapse and heavy use are driven by negative consequences of withdrawal and by development of habitual (i.e. reward/outcome-independent) use. Recent studies indicate that alcohol exposure increases habitual behaviors, including habitual alcohol seeking and drinking, and that this occurs within the first few weeks of moderate alcohol exposure or intake. Competing control of outcome-sensitive and habitual behavior involves interactions between associative and sensorimotor cortical-basal ganglia circuits. Within these circuits. the dorsomedial striatum (DMS in rodents, caudate nucleus in primates) and the dorsolateral striatum (DLS in rodents, putamen in primates) are key brain regions that control outcome-sensitive and habitual behavior, respectively. We have examined the effects of acute and chronic alcohol exposure on synaptic transmission at synapses onto the medium spiny projection neurons (MSNs), the major neurons in this brain region that control output to downstream basal ganglia regions. In this presentation, alcohol-induced changes in synaptic plasticity at glutamatergic corticostriatal synapses, and changes in GABAergic synaptic transmission within the striatal microcircuitry in both DMS/caudate and DLS/putamen will be described. These findings come from studies in both rodent and non-human primate brain. The net effect of these synaptic adaptations is to "disinhibit" the DLS/putamen, and the possible contribution of this process to development of habitual alcohol seeking and drinking will be discussed.

Dopaminergic hypofunction in alcohol dependence: from rodents to humans. M. Diana MD PhD. “G.Minardi” Laboratory of Cognitive Neuroscience, Dept. of Chemistry and Pharmacy, Univ. of Sassari, Italy. Dopamine is an important mediator of the reinforcing effects of drugs of abuse, and alterations in dopamine function might be involved in drug addiction. In particular, basic studies have documented a reduction in the electrophysiological activity of dopamine neurons in alcohol, opiate and cannabinoid dependent rats. Further, dopamine release in the Nucleus Accumbens (Nacc) is decreased in, virtually all, drug-dependent rodents. In parallel, these studies are supported by increments in Intracranial Self Stimulation (ICSS) thresholds during withdrawal from alcohol, nicotine, opiates and other drugs of abuse thereby suggesting a hypofunction of the neural substrate of ICSS. Accordingly, morphological evaluations of the Nacc show profound changes in structure and function of the entire mesolimbic system. On the other hand, human imaging studies have shown a reduction of dopamine receptors in the ventral striatum of cocaine and alcohol dependent subjects thereby offering a visual proof of the "impoverished", addicted human dopamine system. The reduction in physiological activity of the dopamine system leads to think that an increment in its activity may yield clinical improvements. The various possibilities i.e. pharmacological and non pharmacological such as Trans-Cranial Magnetic Stimulation will be discussed.

Altered long-term plasticity of glutamatergic synapses in the nucleus accumbens of alcohol-dependent rats. Enrico Sanna1,2, Valentina Licheri1, Gabriele Sarigu1, Giovanni Biggio2, Giuseppe Talani2. 1Dept of Life and Environmental Sciences, Sect of Neuroscience and Anthropology, University of Cagliari, and 2C.N.R. Institute of Neuroscience, Cagliari, Italy. Alcohol dependence involves complex neuroadaptive processes occurring in discrete brain regions, such as the mesolimbic system, which comprises the ventral tegmental area (VTA) and nucleus accumbens (NAc). Such neuroadaptive modifications, in turn, are thought to involve long-term morphological and functional plasticity of excitatory glutamatergic synapses, and are considered relevant for determining certain behavioral responses, such as positive response to the alcohol experience, craving, withdrawal symptoms that emerge following abrupt interruption, and relapse after prolonged withdrawal. We recently reported that NMDAR-dependent

long-term depression (LTD) was selectively and dramatically reduced in the NAc shell of alcohol-dependent rats that were subjected to 12 h withdrawal. In MSNs the same animals, we also found an altered glutamatergic signaling (reduced NMDA/AMPA ratio) and increased membrane excitability. Interestingly, we have now gathered evidence that treatment of alcohol-dependent rats, tested after 12 h withdrawal, with L-DOPA (6 mg/kg) 1 h before sacrifice, was able to reverse the loss of LTD. In addition, bath-perfusion (for 5 or 30 min) of acute NAc slices obtained from alcohol-dependent rats, after 12 h withdrawal, with dopamine (10 μM) restored the levels of LTD and NMDA/AMPA ratio to the values that were observed in control and alcohol-dependent rats tested while still intoxicated. Furthermore, the D1 antagonist SCH SCH23390, but not the D2 antagonist sulpiride, blocked the effect of dopamine in reversing alcohol-withdrawal induced changes in both LTD and NMDA/AMPA ratio, suggesting that D1 receptors are primarily involved in the alterations in synaptic plasticity produced by withdrawal in alcohol-dependent rats. Moreover, the treatment of alcohol-withdrawn rats with the GABA-A receptor modulator diazepam (5mg/kg), 1 h before sacrifice, failed to alter the loss of LTD formation. These findings suggest that restoration of D1-mediated dopamine signaling in NAc shell of alcohol-dependent rats is effective in preventing crucial neurochemical and functional alterations that are associated with withdrawal. Funded by grant CRP3_63 LR //2007 – Bando 2010 from Regione Autonoma della Sardegna.

Acute and long-lasting changes in neurotransmission in rat striatal subregions by ethanol. Louise Adermark, Addiction Biology Unit, Sahlgrenska Academy, University of Gothenburg, Sweden. Drug addiction is a chronic relapsing disorder that has been linked to progressive neuroadaptations of cortico-striatal networks. Defined subregions of the striatum appear to be selectively recruited during specific stages of addiction, where the ventral striatum (nucleus accumbens, nAc), is associated with the rewarding and reinforcing effect displayed by drugs of abuse, while the dorsal striatum has been implicated in compulsive drug use and relapse. Using in vivo microdialysis and ex vivo electrophysiology, the aim of this project was to define selective effects displayed by acute and repeated exposure to ethanol on neurotransmission in striatal subregions in rodent, with special emphasis on the role of GABAA receptors. In vivo microdialysis revealed that local administration of ethanol enhances extracellular dopamine levels in a manner that is more sensitive to GABAA receptor inhibition in nAc, as compared to the dorsal striatum. Electrophysiological recordings, however, show that ethanol displays a differential impact on excitatory neurotransmission in the two subregions, and that these effects are selectively blocked by the GABAA receptor antagonist bicuculline in the nAc. Conversely, following prolonged voluntary ethanol consumption (>2 months), synaptic output and GABAergic neurotransmission was only suppressed in the dorsal striatum. In the last sets of recordings neuronal firing in selective subregions were studied in relation to the amount of ethanol consumed. Accumbal neurotransmission did not correlate with consumption, but in the dorsal striatum, both synaptic output and bicuculline-induced disinhibition was more pronounced in animals consuming high levels of ethanol. The data presented here suggests a differential impact on acute and long-term ethanol exposure on defined striatal subregions, which could be important for understanding the transition from recreational use towards compulsive alcohol abuse.

GABA-A drugs, addiction and neuroplasticity. Esa R. Korpi, Elena Vashchinkina. Department of Pharmacology, Faculty of Medicine, FI-00014 University of Helsinki, Helsinki, Finland. In the ventral tegmental area (VTA) of the midbrain, a single dose of ethanol induced glutamate neuroplasticity in dopamine neurons of midbrain slices at 24 h after administration, as do many other drugs of abuse including the benzodiazepines diazepam, midazolam and zolpidem, the opioid morphine and the stimulant cocaine. Interestingly, behavioral effects of ethanol resemble those of the neurosteroid agonist ganaxolone and GABA-A direct agonist THIP (gaboxadol), which target especially the extrasynaptic □ subunit-containing GABA-A receptors. These compounds also induced a similar glutamate neuroplasticity in VTA dopamine neurons 1-6 days after a single dose. However, these compounds were poorly rewarding in mice, while alcohol induces both self-administration and place preference. Acutely THIP induced transient sedation, but in wild-type mice a single neuroplasticity-inducing dose of THIP provoked anxiety-like withdrawal state after 2 h in open field and light-dark exploration tests. Plasma corticosterone levels were increased after THIP administration in wild-type mice, with lower levels being found in GABAA

receptor δ subunit-knockout (δ-KO) mice mice. CP 154,526, a selective antagonist of corticotropin-releasing factor CRF1 receptors, reversed both THIP-induced CPA in 4-day place condition test and VTA dopamine neuron plasticity in ex vivo patch-clamp determinations using midbrain slices. Finally, THIP treatment activated the oval part of the Bed Nuclei of Stria Terminalis (ovBNST) in wild-type mice, but not in δ-KO mice, when c-Fos immunohistochemistry was used to detect brain regional activation 2 h after THIP. These results suggest the stimulation of the ovBNST underlies the delayed anxiogenic/aversive state after pharmacological activation of extrasynaptic GABAA receptors. CRF1 receptor activation was involved in the induction of VTA dopamine neuron plasticity and in the expression of conditioned aversion, providing a link from stressful events and motivational processes to adaptive changes in dopamine neurons.

4:00-5:00 ***Colliculo-pulvinar pathway: The fast and coarse road for biologically relevant stimuli in primates.*** Chair: Rafael Maior.

Emotion perception without visual cortex: functional and anatomical mechanisms. Marco Tamietto. Tilburg University, The Netherlands. University of Torino, Italy. Destruction of the visual cortex leads to clinical blindness, but several visual functions may persist without awareness (blindsight). Affective blindsight refers to the uncanny ability of such patients to discriminate reliably the emotional valence of stimuli they cannot consciously perceive. Recent studies have started to examine and compare emotion recognition with and without awareness. This line of research is revealing: a) which behavioral and psychophysiological properties are characteristic of each mode of perception, and b) which neurofunctional and neuroanatomical pathways underpin affective blindsight. As far as the first issue is concerned, emotional stimuli projected to the blind field elicit spontaneous facial expressions and psychophysiological changes that are faster and more pronounced than the reactions triggered when the very same stimuli are displayed to the intact visual field. Also, not all types of expressions can be discriminated without awareness, but only biologically primitive expressions (i.e., basic emotions). Secondly, emotion recognition without awareness and visual cortex seems uniquely associated with activity in a subcortical pathway of ancient evolutionary origin and involving the superior colliculus, the pulvinar and the amygdala. A quantitative voxel-wise meta-analysis on fMRI studies investigating nonconscious emotion perception in healthy participates supports the conclusions drawn on brain-imaging works in patients with cortical blindness. Lastly, in vivo tractography (DTI) shows that these subcortical structures have direct anatomical connections in the intact human and non-human brain and that such connections are strengthened in patients with affective blindsight.

Interaction between the primate deep layers of superior colliculus and the amygdala: Behavioral effects and anatomical connections. Ludise Malkova1, Richard C. Saunders2, Patrick Forcelli1. 1Georgetown University Medical Center, Washington, DC, USA, 2Laboratory of Neuropsychology, NIMH, Bethesda, MD, USA. The superior colliculus has been extensively studied in the nonhuman primate with respect to visual orienting and eye saccades. Whereas the superficial layers of this structure are predominantly visual, the intermediate and deep layers of the superior colliculus (DLSC) are involved in occulomotor activity and threat-related motor behaviors. Extensively studied in rodents, DLSC, together with other structures including the amygdala, constitutes part of the neural circuitry underlying defensive behaviors. We recently found in primates that disinhibition of DLSC evokes defensive behaviors similar to those in rats and these behaviors are modulated by inhibition of the amygdala. In addition, the superior colliculus constitutes a node in the pathway of detecting threat. Neuroimaging data in human subjects suggest functional and anatomical connectivity between the superior colliculus, pulvinar, and the amygdala as a subcortical pathway that is involved in fast and non-conscious perception of emotional stimuli (e.g. facial expressions). In rodents, anatomical studies have revealed the presence of a tectopulvinar pathway that may relay information to the amygdala. Similarly, in a lower-order primate, the tree shrew, the tectopulvinar pathway appears to relay non-topographic visual information from SC through the pulvinar to the amygdala. However, this pathway has not been yet confirmed by anatomical studies in primates. Our anatomical data based on retrograde tracers placed in the amygdala and

anterograde tracers in the colliculus showed a region of sparse overlap of these two projections within the medial pulvinar. This finding is consistent with those in other species, supporting the idea that pulvinar is a part of a subcortical route for visual information to reach the amygdala. Our recent experiments concentrate on the effects of pharmacological manipulations of the colliclus - pulvinar – amygdala pathway on processing of emotional stimuli (including fear-provoking stimuli, e.g. snakes). Behavioral effects resulting from reversible pharmacological manipulations within the circuitry together with anatomical data will be reviewed. Funding: R01MH099505.

Of friends and foes: Threat detection at the ontogenesis of social cognition. Rafael S. Maior; Carlos Tomaz. University of Brasilia, Brazil. Converging lines of investigation have implicated the superior colliculus and the pulvinar nucleus of the thalamus in the processing of affective stimuli in primates. The kind of stimulus that induce activation of these regions has critical survival relevance as they generally include both social and threatening features. The colliculo-pulvinar pathway seems to be especially sensitive to faces and snake images. Our results, based on electrophysiological and behavioral studies, indicate that this subcortical visual pathway play a key role in the fast detection of both threat and social behaviors early on in the primate development. Later on, as the primate brain matures, visual social cues are processed in a more complex mechanism, which might limit the role of the colliculo-pulvinar pathway. On the other hand, its relevance to detect threats seem to be more relevant throughout life. In the present talk, the implication of these results and characteristics of these stimuli will be discussed under an evolutionary perspective. Acknowledgements: National Council for Scientifc and Technological Development (CNPq-Brazil).

Rapid detection of snakes and faces in the monkey superior collicular and pulvinar neurons in the subcortical visual pathway. Hiroshi Nishimaru, Quan Van Le, Minh Nui Nguyen, Jumpei Matsumoto, Yusaku Takamura, Taketoshi Ono, Hisao Nishijo. System Emotional Science, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama. The superior colliculus (SC) and pulvinar are thought to function as a subcortical visual pathway that bypasses the striate cortex and to detect snakes and fundamental facial information. We recorded neuronal responses in the SC and pulvinar of monkeys during a delayed nonmatching-to-sample task, in which the monkeys were required to discriminate various visual stimuli including snakes, monkey and human facial photos, monkey hands, face-like patterns, etc. The results indicated that both SC and pulvinar neurons responded faster and stronger to snakes than monkey faces, monkey hands, and simple geometrical figures. Furthermore, multidimensional scaling (MDS) analyses of the population data indicated that SC and pulvinar neurons detected snakes in early response latencies. Second, SC and pulvinar neuronal responses to human facial photos were analyzed by MDS analyses. The results indicated that population coding by neurons in both the SC and pulvinar classified some aspects of facial information, such as face orientation, gender, and identity, of the facial photos during 50–100 ms after stimulus onset. The Euclidean distances between all the pairs of stimuli in the MDS spaces in the SC were significantly correlated with those in the pulvinar, which suggests that the SC and pulvinar function as a unit. However, in contrast with the known population coding of face neurons in the temporal cortex, the facial information coding in the SC and pulvinar was coarse and insufficient. Identity was face orientation-dependent in the subcortical system, and the left and right profiles were not discriminated in the subcortical system. Furthermore, gaze direction information was not extracted in the SC and pulvinar. These results suggested that the SC and pulvinar, which comprise the subcortical visual pathway, send coarse and rapid information on snakes and faces to the cortical system in a bottom-up process.

5:00-6:00 ***Oral Session 4. Affective Disorders.***

Gestational stress and fluoxetine treatment differentially affect plasticity, methylation and serotonin levels in the PFC and hippocampus of the rat dam. Jodi L. Pawluski1,2,4, Ine Rayen2, Eva van Donkelaar2, Tiffany Loftus1, Harry W Steinbusch2, Nikolaos Kokras3, Christina Dalla3 and Mary Gemmel1. 1Department of Biological Sciences, Ohio University, Athens, Ohio, USA, 2Department of Neuroscience, Maastricht University, Netherlands, 3 Department of Pharmacology, Medical School,

University of Athens, Greece, 4 IRSET INSERM UMR1085, University of Rennes 1, France. Women are more likely to develop depression during childbearing years with up to 20% of women suffering from depression during pregnancy and in the postpartum period. Increased prevalence of depression during the perinatal period has resulted in frequent selective serotonin reuptake inhibitor (SSRI) antidepressant treatment; however the effects of such medications on the maternal brain remain limited. Therefore, the aim of the present study is to investigate the effects of the SSRI medication, fluoxetine, on neurobiological differences in the maternal brain. To model aspects of maternal depression, gestational stress was used. Sprague-Dawley rat dams were exposed to either gestational stress and/or fluoxetine (5mg/kg/day) to form the following four groups: 1. Control+Vehicle, 2. Stress+Vehicle, 3. Control+Fluoxetine 4. Stress+Fluoxetine. At weaning maternal brains were collected. Main findings show that gestational stress alone increased synaptophysin and serotonin metabolism in the CG2 region of the cortex while fluoxetine treatment after stress normalized these effects. In the hippocampus, fluoxetine treatment, regardless of gestational stress exposure, decreased both global measures of methylation in the dentate gyrus, as measured by Dnmt3a immunoreactivity, as well as serotonin metabolism. No further changes in synaptophysin or Dnmt3a immunoreactivity were seen in the cortical or hippocampal areas investigated. These findings show that gestational stress and SSRI medication affect the neurobiology of the maternal brain in a region-specific manner. This work adds to a much needed area of research aimed at understanding neurobiological changes associated with maternal depression and the role of SSRI treatment in altering these changes in the female brain. Acknowledgements: JLP was funded by a Charge de recherche position from the F.R.S.-FNRS in Belgium and is presently funded by a Brain & Behavior Foundation NARSAD Young Investigator Grant.

Positive reinforcing and anxiolytic effects of oxytocin microinjection in the rat central nucleus of amygdala. László K.1, Kovács A. 1, Zagoracz O. 1, Ollmann T. 1, Péczely L.1, Kertes E.1, Karádi Z. 1,2, Lénárd L.1,2. 1Institute of Physiology, University of Pécs, Medical School, Pécs, Hungary, 2Molecular Endocrinology and Neurophysiology Research Group, University of Pécs, Szentágothai Research Center, Pécs, Hungary. The nonapeptide oxytocin (OT) is known to modulate wide variety of behavioral processes like anxiety, cognition and social behaviour. The central nucleus of the amygdala (CeA), part of the limbic system, plays an important role in learning, memory, anxiety and reinforcing mechanisms. The rat CeA was demonstrated to be rich in OT-receptors (OTR). The aim of our study was to examine the possible effects of OT and OTR antagonist administered into the CeA 1) on reinforcement tested by means of the conditioned place preference (CPP) test and 2) on anxiety using the elevated plus maze (EPM) test. Adult male Wistar rats were microinjected bilaterally with 10 ng OT or 100 ng OT (Sigma: O6379, injected in volume of 0.4 µl) or 10 ng OTR antagonist (Sigma: L-2440) alone, or OTR antagonist 15 min prior to 10 ng OT treatment or vehicle solution into the CeA. In the CPP test, rats receiving 10 ng OT spent significantly more time in the treatment quadrant during the test session, while 100 ng OT treatment produced no effect. Pretreatment with the non-peptide OTR antagonist blocked the effects of OT. The antagonist in itself did not influence the place preference. It has been revealed in the elevated plus maze test that 10 ng OT significantly increased the time spent in the open arm. The present study demonstrates that OT in the rat CeA elicits place preference in the CPP paradigm and it has anxiolytic effects in the EPM test. OTRs play a role in the OT induced positive reinforcing and anxiolytic effects since the OTR antagonist blocked these actions. Further experiments are required to show the exact mechanisms through which these behavioral effects are exerted. Supported by: PTE-AOK-KA-2015-15.

Corticosterone induces depressive-like behavior in juvenile female post-pubescent rats, but not pre-pubescent rats. Department of Pharmacology, KCOM, AT Still University, Kirksville, MO. Tyler R. Nickle, Erica M. Stanley, Teresa J. Meyer, and David S. Middlemas*. The aim of this study was to determine the effect of chronic corticosterone (CORT) administration on pre- and post-pubescent juvenile rats in order to develop a rat model of depression in these age groups. Methods: Female rats were administered daily injections of CORT for twenty-one days. Depressive-like behavior was assessed using the modified forced swim test (FST) and the sucrose preference test (SPT). Immunohistochemistry was used to determine associated changes in mitogenesis and newborn neuron survival in the dentate gyrus

of the hippocampus. Results: Female post-pubescent rats injected with CORT showed changes in depressive-like behavior and mitogenesis in the granule cell layer of the dentate gyrus. Furthermore, there was an inverse correlation between time spent immobile and mitogenesis in the dentate gyrus of post-pubescent rats. This was not observed in pre-pubescent rats. Conclusion: These results suggest that CORT treatment may serve as a model of MDD in female post-pubescent rats. Moreover, there may be developmental differences in the effect of CORT that may involve ovarian hormones. Finally, depressive-like behavior measured by the FST is associated with a decrease in hippocampal mitogenesis in female post-pubescent rats, which will lead to experiments testing the role of hippocampal mitogenesis on CORT induced depressive-like behavior.

Sex-dependent behavioral effects of isolation-rearing. F. Scott Hall, Dawn Muskiewicz, Dankesh Joshi, Federico Resendiz Gutierrez, Natasha Hall, Yasir Saber. Dept. Pharmacol. & Exp. Therapeutics, Coll. Pharm. & Pharm. Sci., Univ. of Toledo, OH, USA. Background: Social isolation of mice after weaning (isolation-rearing) has been suggested to produce a variety of pathological behavior phenotypes. In particular, it has been suggested to produce behavioral impairments indicative of a hyperdopaminergic state (hyperlocomotion and increased responses to psychomotor stimulants), and behavior indicative of reduced serotonin function, anxiety and depressive-like behavior. Some data suggests that males and females respond differently to this experience, and may represent sex-dependent differences in the propensity to develop certain psychiatric conditions. Methods: At the age of 21 days of age, male and female C57BL/6J mice (N=10 per experimental condition) were rehoused singly or in groups of 3-4 mice. Subjects remained in these conditions for 8 weeks. At this time they were subjected to several behavioral tests of anxiety (elevated plus maze, open field, and light-dark test) and to testing for prepulse inhibition of the acoustic startle response (PPI). Results: Sex-dependent effects on some measures of anxiety, but not all measures, were observed in these tests. Most notably, isolation-reared female, but not male, mice spent less time in the center of an open field, indicative of increased anxiety in these mice. Isolation-reared female, but not male, mice also spent significantly more time in the closed arms of the elevated plus maze than socially reared female mice. In the light dark test isolation-reared female, but not male, mice had fewer transitions between the light and dark zones. In contrast to these effects on anxiety, isolation-rearing did not affect PPI in female mice, but did produce reduced PPI (at the lowest pre-pulse intensity) in male mice. Discussion: The present experiments found evidence that the effects of isolation-rearing are sex-dependent. (1) Isolation-reared female, but not male, mice were less active in the center of an open-field, indicative of increased anxiety. (2) Isolation-reared male, but not female mice, had deficits in PPI, an animal model of sensorimotor gating indicative of hyperdopaminergic function. Collectively, these data suggest that early social isolation has distinctly different effects in male and female mice.

Individual variability in mice' response to lithium: a hurdle or an advantage? Itamar Ezer1 Catherine Belzung2 Haim Einat1,3,4. 1School of Behavioral Sciences, Tel Aviv-Yaffo Academic College, Tel-Aviv; 2INSERM 930 & Department of Neurosciences Université François-Rabelais de Tours ; Dept. of Clinical Biochemistry and Pharmacology, Ben-Gurion University of the Negev, Beersheba; 4College of Pharmacy, University of Minnesota, Duluth MN. Individual variability in response to mood stabilizing drugs poses a significant hurdle in the treatment of bipolar patients. There is a well-known heterogeneity in the response of patients to treatment and many patients are partial or non-responders. Differences in response might be related to genetics but to date specific findings are inconclusive. Accordingly, animal models may be one important venue to advance the study of individual variability in response to drugs. Individual variability in animal models is well noted in all contexts of research and had been studies mostly in the context of animal physiology and ecology. Yet, in studies related to disease and treatment individual variability is usually treated as a limiting factor and is dealt with by standardization and by increasing the number of animals per group. Although the general tendency is to try and overcome variability, it is also possible to utilize heterogeneity in animals to explore the biology of individual variability in humans. In that context, initial work in our laboratory clearly demonstrates the heterogeneity in mice response to lithium in both models of depression and mania. Our data show that similar to patients, about one third of mice show strong response, about one third show intermediate response and

about one third show no response to chronic drug administration. These diverse effects are demonstrated in both ICR and black Swiss mice. Current work in the lab is aimed at exploring physiological, biochemical and molecular correlations to the behavioral responses to lithium. Such correlations may support the attempts to predict response in models and possibly in patients and advance the development of personalized medicine in bipolar disorder.

Integrity of Parent's Brain in Infancy Supports the Development of Children's Social Competencies. Eyal Abraham1, Talma Hendler2,3, Orna Zaggory-Sharon1; Ruth Feldman1,4. 1Psychology and Gonda Brain Research Center, Bar Ilan university, Ramant Gan, Israel; 2Functional Brain center, Wohl Institute of Advanced imaging, Tel-Aviv Sourasky Center, Tel aviv, Israel; 3School of Psychological Sciences, Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University, Tel aviv, Israel; 4Child Study Center, Yale University School of Medicine, New Haven, CT, USA. Studies in animal models demonstrate that the cross-generation transmission of mammalian sociality begins with plasticity of the parent's brain in the postpartum; such plasticity triggers expression of the species-typical parenting behaviors, which, in turn, organize infant brain and behavior to life with others. No study, however, has tested such cross-generational sequence in humans and charted its progression from integrity of the parental brain in infancy to the emergence of core social competencies in human children.

We measured brain response of 45 primary-caregiving parents to their infant's stimuli, observed parent-infant synchrony, and assayed parental oxytocin (OT). Intra- and inter-network connectivity were computed in three main networks of the human parental brain - core-limbic, embodied-simulation/empathy, and mentalizing. In preschool, two key child social competencies were observed: emotion-regulation and socialization and micro-coded. Degree of network integrity in parent's brain predicted children's social outcomes, with subcortical and cortical network integrity foreshadowing mammalian-general versus human-specific competencies. Parent-infant synchrony mediated the links between connectivity of parent's embodied-simulation network and preschoolers' ability to use cognitive/executive emotion regulation strategies, highlighting the inherently dyadic nature of this network and its long-term effects on tuning young to social life. Parent's inter-network core-limbic-embodied-simulation connectivity predicted children's OT as moderated by parental OT. Our study is the first study in humans to chart longitudinal links from network integrity of the parent's brain in infancy and two critical child social skills in preschool, suggesting how the parent-infant interface provides the template for species continuity and evolutionary change via reciprocal social behavior. Our findings demonstrate how connectivity of the parent's brain in specific and specialized neural circuits profoundly affects their children's social development, predicting two key social competencies in preschoolers – emotion regulation and socialization. Conceptually, by demonstrating the fundamental social embeddedness of the human brain, our findings challenge the solipsistic theoretical stance underpinning most current neuroscience research and may contribute to narrowing the gap between the brain of one individual and that of other social beings. We further suggest that investigation of human parenting, as the prototypical context for such embeddedness that carries profound effects for offspring’s survival and thriving, functions as a complex brain-behavior-environment system.

5:00-6:00 ***Oral Session 5. Other Systems and Behavioral Effects.***

Exploring the Causal Link Between Ultrasonic Vocalizations and Behavior in Rats. Candace Burke1, Theresa M. Kisko2 , Sergio M. Pellis1 , David R. Euston1 1 Dept 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 but the calls tend to be significantly more diverse. In fact, it has been suggested that there are as many as 14 distinct call types. To date, no detailed study of the specific behavioral correlates of these many different call types has been published. The goal of our study is to determine the specific behavioral context

leading to each call type. Our first study looked at vocalizations from single animals while they were expecting play, a situation associated with a large number of 50kHz calls. Using simultaneous video and audio recordings, we manually coded the exact time of occurrence of every behavior and every vocalization. A Monte-Carlo shuffling procedure was used to identify vocalization behavior correlations that were statistically significant. We found that active behaviors such as walking, running and jumping were strongly correlated with vocalizations while resting, exploration and rearing where not. Walking was strongly associated with calls including a trill while running and jumping were more strongly associated with calls made up of multiple components, including flats and blips. Our second study involved pairs of rats, one vocal and one devocalized, engaged in playful interactions. Again, we found specific calls tied to specific behaviors, with more vocalizations during active states versus exploration and rest. In general, we found that the initiator of the behaviors tended to be the one vocalizing. Following, chasing, and nape attacks were strongly associated with vocalizations when the vocal rat was the protagonist rather than the recipient. Active attempts to escape being pinned were also associated with specific calls while passive behavior was not. These results indicate that specific calls are emitted during particular moments during both exploration and during social interactions, suggesting that they serve a role in coordinating sequences of action. Supported by NSERC (Discovery Grant) and Alberta Innovates Health Solutions.

Closed nest pre-weaning environment improves the development of physical characteristics and reflexes in neonatal hypoxic ischemic injury. S Tiffany Donaldson, PhD1, Laura Grace Rollins, BS1, Hayley Santolucito, BA1, Rebecca Ravenelle, BA2, and Briana Mason1. 1Developmental and Brain Sciences, Department of Psychology, University of Massachusetts Boston, 100 Morrissey Boulevard, Boston, MA, 02125 USA, 2 City University of New York, CUNY Neuroscience Collaborative, The Graduate Center, 365 Fifth Ave., New York, NY 10016 USA. Term neonates with hypoxic-ischemic (HI) injury are at risk for devastating neurological sequelae. Maternal care taking behavior has been found to alter the trajectory of normal brain development and may also impact neurodevelopment with exposure to HI injury. Care-taking behavior can be highly influenced by environmental stress and may, therefore, mediate the effects of such stressors on injury and repair for these neurologically high-risk neonates. We investigated whether altering early environment for maternal care-taking impacts neurodevelopment, cognitive learning, and hippocampal neuroprotection in HI offspring. The Rice-Vannucci model was used to induce HI in 26 postnatal day (PND) 7 Long-Evans pups. Litters were randomized to a closed nest (CN) or normal animal facility (AF) condition. Performance on a neurodevelopmental battery and characteristics of physical development were assessed daily from PND8-PND21 to quantify effects of the CN condition. Animals reared in the CN condition exhibited significantly earlier development of physical characteristics, exhibiting ear unfolding an average of 2.23 days earlier ($p<0.001$), eye opening 1.85 (L) and 1.07 (R) days earlier ($p<0.001$), left ear twitch 1.9 days earlier ($p=0.037$), and audible startle response 1.46 days earlier ($p=0.005$) than those in the AF condition. There was also a trend observed for earlier development of negative geotaxis ($p=0.084$) in CN condition by 2 days. In addition, animals in the CN condition were consistently found to have a significantly higher body weight than those in AF ($p<0.001$) throughout the pre-weaning period. CN reared rats also displayed increased spatial learning and memory in the Morris Water Maze, greater ipsilateral hippocampal volume and glucocorticoid receptor expression. These findings indicate that, in comparison to AF housing, CN housing during the pre-weaning period improves the development of reflexes and physical characteristics, cognitive performance and hippocampal integrity in pups exposed to neonatal HI.

The putative lithium-mimetic ebselen reduces impulsive action but not impulsive choice. Chris Barkus1,2, Jacqueline-Marie Ferland2, Wendy Adams2, David Bannerman1, Catherine Winstanley2, Trevor Sharp1. 1University of Oxford, UK. 2University of British Columbia, Vancouver, Canada. Lithium remains the frontline treatment for bipolar disorder despite its poor tolerability and plethora of side effects due to a lack of effective alternatives, particularly in reducing suicidal behaviour. Lithium is also effective at reducing other impulsive behaviours such as pathological gambling. The mechanism by which lithium exerts its clinically desirable effects is unknown, but the best candidate is its blockade of inositol monophosphatase (IMPase), a key enzyme in the second messenger system of Gq-coupled metabotropic receptors such as the 5-HT2 family of 5-HT receptors. 5-HT2A and 5-HT2C receptors have

been shown to have powerful and reciprocal effects on impulsive behaviour, with increases in 5-HT2A-mediated activity leading to increased impulsivity and, conversely, greater 5-HT2C-mediated activity leading to reduced impulsivity. Ebselen has been identified as a selective blocker of IMPase activity and may therefore act as a functional antagonist to 5-HT2A receptors and so reduce impulsivity in a manner similar to lithium. Ebselen was identified from a screening of drugs that have previously been in Phase III clinical trials and is therefore known to be well tolerated in humans. If ebselen can be demonstrated to effectively reduce impulsivity preclinically it would advance its candidacy as a safer alternative to lithium in the treatment of bipolar disorder and other impulsive control disorders. We tested acute doses of ebselen administered ip. one hour before testing in several models of impulsivity and decision-making in rats. This included the 5 choice serial reaction time task (5CSRTT), an attentional test that allows for the measure of impulsive responses, delay discounting as a test of impulsive choice behaviour, and the rodent gambling task (rGT). Furthermore, we assessed the ability of ebselen to block “wet dog shakes” induced by the 5-HT2A agonist 2,5-Dimethoxy-4-iodoamphetamine (DOI). We found that ebselen reduced premature responding in both the 5CSRTT and rGT, the principle measure of impulsive action in both tasks. However, ebselen had no effect on choice behaviour in either the rGT or delay discounting tasks. Ebselen effectively blocked DOI-induced shakes, a behavioural measure of 5-HT2A receptor activity. Collectively, these data suggest ebselen may be effective in reducing impulsive behaviour clinically and that this may be due to functional inhibition of the 5-HT2A receptor. This work is funded by the UK Medical Research Council.

Early-life inflammation decelerates fear extinction in adult rodents – Potential implications for the endocannabinoid system. Doenni, Vienna M1; Hill, Matthew N1; Pittman Quentin J1. 1University of Calgary. Inflammation is one of the most common physiological stressors. While inflammation is a normal mechanism to clear pathogens, there is now emerging evidence that it can have substantial effects on development. In recent studies our lab discovered a susceptible window during which a single exposure to the bacterial endotoxin lipopolysaccharide (LPS) can cause long lasting changes in physiological and behavioral processes. To date the impact on anxiety related traits, substantially mediated by the amygdala, have not been determined. In the presented research we will address the hypothesis that a single postnatal LPS challenge causes long lasting alterations in amygdala-associated behaviors. It has previously been shown that general anxiety test such as open field behavior or behavior within an elevated plus maze are unaffected by P14 LPS. Early-life inflammation induced behavioral changes are more subtle and are frequently connected to behaviors know to be strongly mediated by endocannabinoids (e.g. social behavior or novelty induced suppression of feeding). Therefore we hypothesized that the extinction of a fearful memory cued by an auditory stimulus, a process highly dependent on amygdaloid cannabinoids, is altered (decelerated) by early-life inflammation. To that aim Sprague Dawley rats were bred in our facilities and treated on postnatal day (P) 14 with either 100µg/kg LPS or an equal volume of saline. On ~P60 animals were fear-conditioned to an auditory cue and subsequently subjected to a 2-day extinction protocol. Our experiments revealed delayed fear extinction on extinction day 1 in LPS injected animals in a repeated measure ANOVA design ($F(1,21) = 15.96$, $p < .01$). Acquisition and reaction to the stimulus on day 2 were unaltered in P14 LPS treated animals. Due to the specific nature of the alteration and a previously established connection between P14 LPS and fatty acid amide hydrolase (FAAH) activity and endocannabinoid profiles in the amygdala, we hypothesized that by augmenting anandamide with a FAAH inhibitor (administered orally) we may be able to facilitate fear extinction in rats that experienced early-life inflammation. Our data indeed confirms this hypothesis, showing facilitation of fear extinction in P14 LPS injected animals but not controls. The findings in this study further elucidate the discussion about different predispositions to anxiety disorders such as posttraumatic stress disorder (PTSD). We believe that early-life inflammation plays a role in predisposing individuals to extended fear retention. Untangling the complicated mechanisms involved could yield the potential for more targeted therapies.

Pharmacotherapy combined with psychotherapy in social disturbances: plastic role of the ventromedial prefrontal cortex. Eva Mikics*1, Nina Karpova*2, László Biró1, Ramon Guirado2, Christina Miskolczi1, Máté Tóth1, Diána Balázsfi1, Dóra Zelena1, Juzoh Umemori2, József Haller#1, Eero

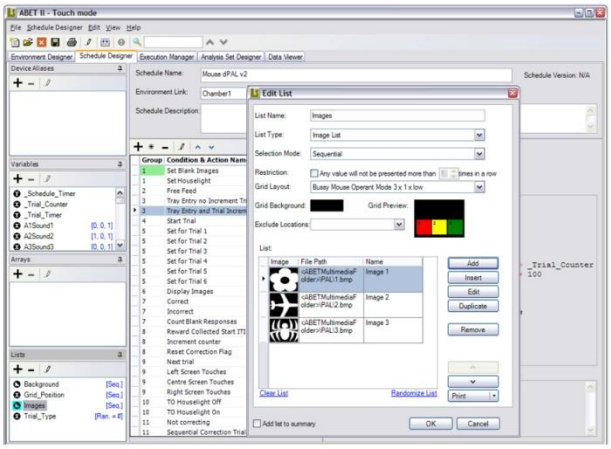
Castrén#2. 1Department of Behavioral Neurobiology, Institute of Experimental Medicine, Budapest, Hungary, 2Helsinki University, Neuroscience Center, Helsinki, Finland, *,# equal contribution. Aversive social environment during childhood including abuse and neglect is selectively associated with later antisociality and criminal behavior, however, the processes that mediate this relationship remain largely unknown. We have earlier demonstrated that post-weaning social isolation of rats – a laboratory modell for early social neglect – resulted in escalated and abnormal forms of aggressiveness and over-activation of several brain regions, including the medial prefrontal cortex (mPFC) during aggressive encounters in laboratory rats. Deficits in prosocial behavior were eliminated by resocialization during adulthood, but abnormal aggression was resilient to this treatment. We assumed that escalated aggression was refractory to the corrective effects of re-socialization because of the adulthood-specific reduction in neural plasticity; therefore, here we investigated whether the neural plasticity-enhancer fluoxetine makes animals receptive to the effects of re-socialization in this model. The hypothesis was tested by combining psychosocial and plasticity-related pharmacological treatments (re-socialization and fluoxetine, respectively) in male rats submitted to post-weaning social isolation. According to our results, post-weaning social isolation induced abnormal and escalated forms of aggression in adulthood that was eliminated by the combination of 3-week long fluoxetine therapy and re-socialization, but neither treatment alone. To study treatment-induced changes in neural plasticity, we investigated gene expression profiles in brain regions relevant for aggression control by qPCR. Re-socialization and fluoxetine, albeit did have independent effects on neural plasticity in some brain regions, interactively modulated neural plasticity in the infralimbic cortex of the mPFC: the expression of BDNF 1 and 4, the epigenetic enzyme DNMT1 and aggression-related MAOA genes were down-regulated by post-weaning social isolation in the infralimbic cortex and restored by the combined but not by individual treatments. In summary, rats submitted to post-weaning social isolation model, fluoxetine dramatically enhanced the effects of re-socialization, indicating a synergistic interaction between positive social experiences and enhanced neural plasticity. The mPFC emerged as important mediator of the beneficial effect. This suggests that aggression problems may be solved by plasticity-related pharmacological treatments to promote the efficacy of psychotherapy.

Application of activation induced manganese-enhanced magnetic resonance imaging (MEMRI) for mapping of brain structures activated by operant behavior in rats. Gálosi, R.1, Szalay, Cs.1, Aradi, M.2,3, Pál, J.2, Perlaki, G.2,3, Karádi, Z.1,4 and Lénárd, L.1,4. 1Institute of Physiology, Medical School of University of Pécs, Hungary, 2Neurosurgery Clinic, Medical School of University of Pécs, Hungary, 3Pécs Diagnostic Center Ltd, Pécs, Hungary, 4Molecular Neuroendocrinology and Neurophysiology Research Group, Szentágothai Research Center, University of Pécs, Hungary. The manganese-enhanced magnetic resonance imaging (MEMRI) utilizes manganese ion accumulation in excitable neurons to detect activated brain areas. The goal of the present experiments was to develop a protocol for the application to extend it for operant condition situation with particular attention to the toxicity of manganese and with the expected advantages for the possible detection of the whole-brain responses to the operant behavior in rodents. $MnCl_2$ was intraperitoneally infused in Wistar rats at a dose of 20 mg/kg or an accumulated dose of 40 mg/kg or 60 mg/kg, respectively. Repeated infusions of 20 mg/kg $MnCl_2$ were separated by 24 h to reach the accumulated doses. Effects of $MnCl_2$ were examined on hepatic, somatosensory and motor functions. Cognitive capabilities of the animals were tested in cued visual discrimination operant task. The MEMRI technique was adapted to a 3T clinical MR scanner. T1 maps were calculated before and after $MnCl_2$ administration followed by cued visual discrimination operant task. Changes in T1 values were compared among brain areas of trained animals participating in the water rewarded operant task and naive control rats. Increased serum total bilirubin, aspartate aminotransferase, alanine aminotransferase concentration and decreased albumin level at the dose of 60 mg/kg $MnCl_2$ indicated hepatotoxic effect, while these parameters were within the normal range after the lower doses. The dose of 20 mg/kg and the 40 mg/kg $MnCl_2$ did not have an effect on the accuracy of operant responding. However, both doses enhanced omissions at the end of the operant session indicating a change in motivation and vigor of operant behavior. At last, the developed MEMRI protocol was able to detect activity in brain areas related to the cued visual discrimination operant behavior. The

following brain areas showed extensively activation compared to control animal: the visual, somatosensory, motor and premotor cortices, the insular, cingular, ectorhinal, entorhinal, perirhinal and piriform cortices, hippocampus, amygdala with amygdalo-hippocampal areas, dorsal striatum, nucleus accumbens core, pars compacta of the substantia nigra and retrorubral field. In conclusion, the method was able in rats to detect brain regions which are involved in the control of visual stimulus related and reinforced operant responses. Also, the MEMRI has proved to be a reliable method to map brain activity in correlation with the behavior in rodents.

6:00 **Early Career Award Presentation. Michael Bowen**, School of Psychology, University of Sydney, Australia. Department of Behavioral and Molecular Neurobiology, University of Regensburg, Germany. Faculty of Pharmacy, University of Sydney, Australia. Oxytocin inhibits ethanol consumption and intoxication in rats: interactions with dopamine and extrasynaptic GABA-A receptors.

Oxytocin inhibits ethanol consumption and intoxication in rats: interactions with dopamine and extrasynaptic GABAA receptors. Bowen, M.T.1, Peters, S.T.2, Absalom, N.3, Chebib, M.3, Neumann, I.D.2, McGregor, I.S.1. 1School of Psychology, University of Sydney, Australia, 2Department of Behavioral and Molecular Neurobiology, University of Regensburg, Germany, 3Faculty of Pharmacy, University of Sydney, Australia. Alcohol is one of the most widely abused recreational drugs and is arguably the most harmful. Current treatment options lack efficacy and a breakthrough in our approach is sorely needed. A growing number of preclinical studies indicate that the neuropeptide oxytocin may have substantial utility in the treatment of alcohol use disorders. Work in the 1980s demonstrated that oxytocin inhibits ethanol tolerance and withdrawal but little further work was conducted on oxytocin-ethanol interactions over the proceeding decade and a half. Our initial studies demonstrated that administration of oxytocin causes a lasting decrease in ethanol consumption and preference in rats. More recently, we have demonstrated that oxytocin effects on alcohol consumption are centrally mediated and we have linked these effects of oxytocin to a hitherto unknown ability of the neuropeptide to reduce ethanol stimulation of the dopamine reward system. While conducting this work we discovered that oxytocin causes a striking inhibition of the acute motor impairing effects of ethanol. Ethanol's effects at extrasynaptic δ subunit-containing GABA A receptors are heavily involved in the motor impairing effects of ethanol, and in ethanol reward and tolerance. Using electrophysiological techniques, we have subsequently demonstrated that oxytocin exerts a highly specific and complete blockade of ethanol actions at these δ subunit-containing GABAA receptors. Furthermore, these effects of oxytocin are due to a direct, non-oxytocin receptor mediated action at δ subunit-containing GABAA receptors. These recent findings therefore indicate that oxytocin substantially interferes with ethanol's primary actions in the CNS, providing novel insights into possible mechanisms driving oxytocin's interference with ethanol ataxia, tolerance and reward.



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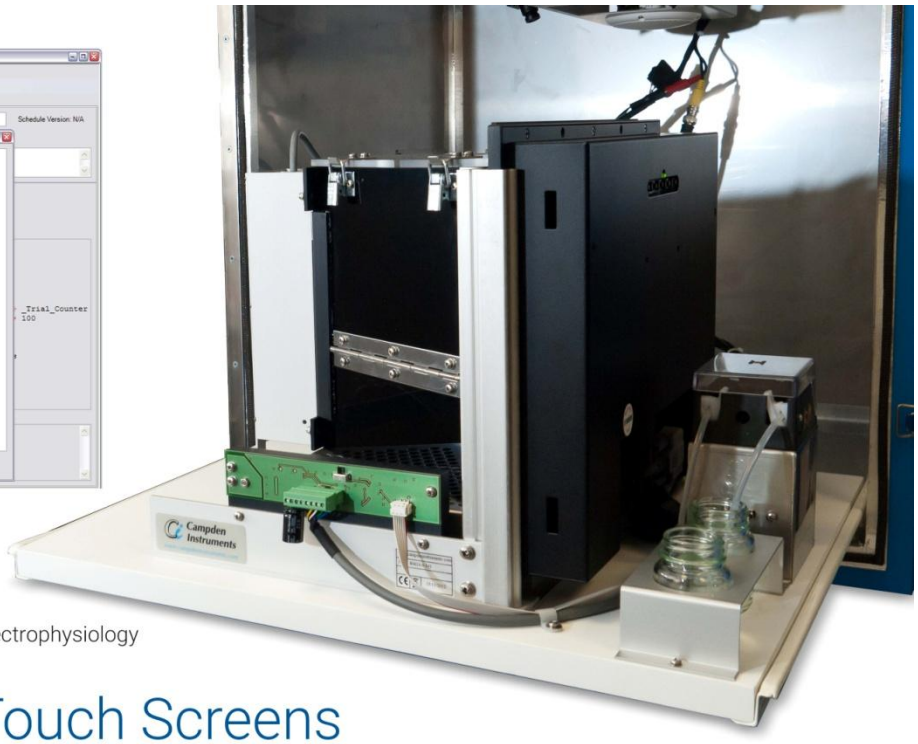

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