IBNS 2020 Online Poster Sessions

Event Schedule

Mon, Aug 03, 2020

IBNS 2021 - A sneak peak

Announcing IBNS 2021 Keynote Speakers:

Marina Picciotto, Yale University
Tracey Shors, Rutgers University
Kay Tye, Salk Institute
Gina L. Quirarte, UNAM

Important Dates:

Symposia Proposals Due - October 1, 2020
Travel Award Applications Due - December 6, 2020
Abstract Deadline - February 3, 2021

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Marianne

Outstanding Achievement Award presented to Mark Geyer

Outstanding Achievement Award

The recipient of this award is chosen by the Nominations and Awards Committee for outstanding professional achievement and consistent and long-standing contributions to the Society.

Deletion of beta2* nicotinic acetylcholine receptors in striatal GABAergic interneurons leads to alterations of behavior in conditional knockout mice.

Deletion of beta2* nicotinic acetylcholine receptors in striatal GABAergic interneurons leads to alterations of behavior in conditional knockout mice. Abbondanza A.1, Höfflin J.1, Elias J.2, Janickova H.11 Department of Neurochemistry, Institute of Physiology, CAS, Prague, Czech Republic2 Laboratory of Transgenic Models of Diseases, Institute of Molecular Genetics of the ASCR, Vestec, Czech RepublicThe importance of striatum

in behavioral control and cognition has been extensively studied, but little is known about the functional role of nicotinic acetylcholine receptors (nAChRs) expressed by striatal GABAergic interneurons (GABAINs). The striatal projecting neurons (SPNs) express low levels of nAChRs, hence the vast majority of striatal nAChRs is expressed on striatal interneurons, either cholinergic (CINs) or GABAergic. We hypothesize that acetylcholine released by CINs activates nAChRs expressed by GABAINs and that this activation is important for modulating striatal-based behavior.To determine the function of nAChRs expressed by GABAINs, we deleted beta2 nicotinic subunit by injecting Cre-expressing AAV viral vector into the dorsal striatum of beta2-flox/flox mice. The mice were tested in a battery of behavioral tasks focused on striatal-based behavior including open field and social preference test, response learning in the cross-maze and the operant box. In addition, neuronal activity markers were evaluated by immunohistochemistry to verify if the beta2 deletion in GABAINs led to changes in activation/inhibition balance in the striatum. Finally, we sought to induce beta2 deletion in specific types of striatal GABAINs using the CRISPR/Cas9 method. Mice with deletion of beta2* nAChRs showed alterations in several behavioral paradigms including hyperactivity and higher anxiety in the open field, less social interaction and impaired response learning in the T-maze.We conclude that beta2* nAChRs expressed by striatal interneurons are important for controlling striatal-based behavior including locomotor activity and learning. However, the exact mechanisms involved in this control are not clear and they need to be further investigated. This work was supported by the Grant Agency of the Czech Republic Grant #19-07983Y. J.H. was supported by DAAD RISE program.

Speaker

Alice Abbondanza PhD student, FGU - Institute of Physiology CAS

Prediction of Real Life Behaviors With the Help of VR Games: a Short Report

Prediction of Real Life Behaviors With the Help of VR Games: a Short ReportAta Pourabbasi 1Amin Akbari Ahangar 1Sarah Nouriyengejeh 1Mohammad Shayan Karamighahi 1Bahare Seyedhoseini 1Amin Shakarami 11 Endocrinology and metabolism research center, endocrinology and metabolism clinical sciences institute, Tehran University of medical sciencesThese days, paper and computer-based tests are the most popular assessment tools for cognitive and behavioral conditions in practice. However, biases of these methods pushed researchers and practitioners to seek assessments that are closer to real-life settings. In-game evaluations, as a near real-life setting, have a high potential to be used as an unbiased, highly accurate, and scalable approach for different cognitive and behavioral assessments. In this pilot study, we tried to design an in-game cognitive and behavioral evaluation protocol using Virtual Reality (VR) technology to assess the physical activity, muscle strength, attention, and concentration in human subjects. Participants were 12 men and women with an average age of 27. Physical activity was measured based on the IPAQ standards. Muscle strength was assessed with a Dynamometer (SH-UM-001, Rev.1, 2012, SAEHAN Corporation, South. Korea). The gold standard for attention and concentration were Selective and Divided Attention tests, v 0.5. The game 'œBeat Saber' (Ver. 1.3) running on the HTC - VIVEâ„¢ system was used as the experiment platform. Data collection was achieved through the customization of OpenVR SDK. The initial results demonstrate a hopeful, positive correlation between in-game movement patterns and physical activity using the Pearson test and possible use for in-game assessments as an accessible, valid evaluation tool to predict physical activity and cognitive ability in near real-life settings.No competing financial interests exist.

Speaker

Amin Akbari Ahangar Researcher/Data Analyst, Endocrinology and Metabolism Research Center

Behavioral pattern and neural activation after repeated social stress in C57Bl/6 mice

Behavioral pattern and neural activation after repeated social stress in C57Bl/6 miceAlmeida, Alisson 1 ; Motta, Simone 11 Institute of Biomedical Sciences of the University of Sao PauloThe confrontation between

animals of the same species for environmental resources, such as food and territory, is common in the animal kingdom. In this sense, social defense strategies are relevant for maintaining the integrity of the group and the individual's survival. Thus, the purpose of this work is to evaluate the behavioral pattern and neural activation after repeated social stress in C57Bl/6 mice. For this, we compared this characteristics among C57Bl/6 mice submitted to 1 exposure (1E,n=7) or 3 exposures (3E,n=11) of the resident-intruder paradigm (CEUA approval #58/2016). The activation was evaluated measuring the density of Fos-labeled cells of the selected regions. In regard to behavior, 3E animals spent more time on passive defense and less time on exploratory behaviors during day 3 of exposure in comparison to 1E group (Exploration, p=0.001; Passive Defense, p=0.001). This change in behavioral pattern is accompanied by less neural mobilization of areas known to be involved in conspecific processing, such as the medial amygdala and nuclei of the hypothalamic sexually dimorphic circuit - such as the ventrolateral portion of the ventromedial nucleus of the hypothalamus
(MeAad:p=0.002|MeApd:p=0.024|MeApv:p=0.002|rVMHvl:p=0.001|cVMHvl:p=0.001|PMV:p=0.001). Furthermore, we did not observe differences in the activation between animals 1E and 3E of the juxtadorsomedial and juxtaparaventricular portion of the lateral hypothalamic area - which could to be involved in contextual processing - as well as of the dorsal premammillary nucleus, important for the expression of passive defensive behaviors. The lower mobilization of structures involved with the processing of social information in 3E animals suggests that social signals are recruited less intensely for the modulation of defensive behaviors through reexposures to the social stress. It is interesting to note that this occurred although the residents were different at each reexposure. The rearrangement of the neural activation pattern, accompanied by a maintenance of the activity of regions that would be associated with the processing of contextual information, might be behind the shift from an active defense strategy to a more passive strategy.Acknowledgment: FAPESP grant #2018/24288-7; #2016/18667-0.

Speaker

Alisson Almeida Undergraduate Student, University of São Paulo

Disruption of Circadian Rhythms through the Genetic and Pharmacological Alteration of REV-ERBÎ± and its Effects on Alcohol Abuse

Disruption of Circadian Rhythms through the Genetic and Pharmacological Alteration of REV-ERBÎ± and its Effects on Alcohol Abuse. Al-Sabagh, Yasmine 1, Jenkins, Bryan 1, Talhat, Asfandyaar 1, Hamidullah, Shahnaza 1, Thorpe, Hayley 1, Martino, Tami 1, Khokhar, Jibran 1. 1 University of Guelph. Circadian rhythms, the body's internal biological clock, play a vital role in the regulation of the timing of many vital processes, and its disruption has been linked to increased substance dependence. The REV-ERBÎ± protein controls the expression of essential clock genes and thus is crucial in maintaining the precision of the circadian timing system. Altered REV-ERBÎ± activity results in altered mood regulation and a hyperdopaminergic state, both of which have been associated with increased alcohol seeking and use. The aim of the study is to investigate the effects of circadian rhythm disruptions on alcohol consumption by altering REV-ERBÎ± receptor activity through genetic and pharmacological manipulation. Moreover, we examine potential sex differences in alcohol consumption in relation to the genetic changes. Two experiments were carried out, one including the genetic alteration and one including the pharmaceutical alteration of the protein. Experiment 1: fifty- six adult mice (WT male (n=7), WT female (n=11), REV-ERBÎ± Knock Out (KO) male (n=5), REV-ERBÎ± KO female (n=11), Het male (n=10) and Het female (n=10)) were housed in pairs using a mesh divider in the cage. Mice were given ad libitum access to 10% ethanol [v/v] and water using a two-bottle choice paradigm. The mice were housed for 22 days on a 12-h light: 12-h dark cycle. Alcohol, food and water consumption as well as body weight were measured every 24 hours. Experiment 2: sixteen WT male were treated with SR8278 (25'‰mg/kg) or vehicle solution for 7 days with the same housing conditions as experiment 1, with access to 10% alcohol in a two-bottle choice design. Repeated measures ANOVA revealed a main effect of genotype where REV-ERBÎ± KO mice consumed less alcohol throughout the study ($F(2,52) = 22.578$, $p<0.05$). There was no significant difference in preference between Het mice and WT mice ($p>0.05$). A main effect of sex was revealed where females consumed more alcohol than males throughout the study, regardless of the genotype ($F(1,52) = 10.576$, $p<0.05$). However, no interaction between sex and genotype on alcohol preference was observed ($F(1,52) = 0.942$, $p=0.404$). In the pharmacological antagonism experiment, no differences were observed between the REV-ERBÎ± antagonist administered group and the vehicle group ($p>0.05$) although a trend toward lower alcohol consumption was observed in the drug group, suggesting that the dose of the drug was a possible limitation. The decreased alcohol preference in REV-ERBÎ± KO mice suggests that the alteration of REV-

ERBÎ± does not result in an increased risk of alcohol use, but in this case results in a decreased risk. Moreover, further experiments should be conducted using the REV-ERBÎ±-antagonist drug at difference doses. Since REV-ERBÎ± is a druggable target, our results could spark the creation of drugs targeting REV-ERBÎ± in the treatment of Alcohol Use Disorder (AUD) and thus reducing the negative health effects associated with AUD.

Speaker

Yasmine Al-Sabagh Undergraduate Student, University of Guelph

Effects of Ashwagandha (Withania somnifera) on Anxiety-like Behavior and Whole-body Cortisol Levels in Adult Zebrafish Exposed to Chronic Crowding Stress

Effects of Ashwagandha (Withania somnifera) on Anxiety-like Behavior and Whole-body Cortisol Levels in Adult Zebrafish Exposed to Chronic Crowding StressRama Alsakaji 1, Noelle Opiola 1, and Maureen L. Petrunich-Rutherford 11Department of Psychology, Indiana University NorthwestAshwagandha, derived from the Withania somnifera root, is reported to have antioxidant, anxiolytic, and antidepressant properties. It is unknown whether ashwagandha attenuates anxiety via stress hormone regulation. The purpose of the current study was to determine if acute exposure to ashwagandha would elicit anxiolytic-like effects on behavior and alter neuroendocrine responses in zebrafish (Danio rerio). Neuroendocrine stress responses in zebrafish are regulated by the hypothalamic-pituitary-interrenal axis, which is homologous to the hypothalamic-pituitary-adrenal axis of mammals. It was hypothesized that ashwagandha would reduce anxiety-like behavior and reduce whole-body cortisol levels in chronically stressed zebrafish. Adult, mixed-sex, wild-type zebrafish (N=80) were divided among 4 groups, with drug and stress as independent variables. Chronic stress exposure was conducted by crowding the fish at a concentration of 10 fish per liter for approximately 2 weeks; control subjects were housed at 5 fish per liter. Fish from both crowded and control conditions were individually transferred to 1-liter tanks for exposure to ashwagandha (2.8 mg/L) or untreated water (1L) for 60 minutes. Subjects were transferred to the novel tank test for 6 min to measure motor and anxiety-like behavioral measures. Cortisol was extracted and quantified with an ELISA. While no variables were significantly altered by stress or drug, there was a marginally significant trend toward reduced anxiety-like behavior in drug-treated fish and a marginally significant interaction between drug and stress for entries to top and whole-body cortisol levels. Thus, ashwagandha has potential to mitigate stress-induced changes in anxiety-related measures. Further studies should investigate other concentrations of ashwagandha, whether there are sex-dependent differences in drug responses, and whether chronic drug treatment influences neuroendocrine and behavioral responses in zebrafish.This study was funded by the Indiana University Northwest Research Support Fund.

Speaker

Rama Alsakaji Indiana University Northwest

Controlling the Brain's Emotional Switch: Biased Cholinergic Input within the Basolateral Amygdala

Controlling the Brain's Emotional Switch: Biased Cholinergic Input within the Basolateral Amygdala Amodeo, John M 1; Vu, Nguyen 1; Jones, Grace C 1; Warren, James W 1; McDonald, Alex J 1; Mott, David D 1 1 University of South Carolina School of Medicine The basolateral amygdala (BLA), made up of the basolateral (BL) and lateral (LA) nuclei, works as the brain's emotional processing center, encoding stimuli with emotional valence. Previous studies indicate valence is assigned via selective excitation of specific BLA pyramidal neurons (PNs) that project to appetitive or aversive behavioral circuits. Two PN populations have been found in the BL, segregated to either the anterior (BLa) or posterior (BLp) subdivisions. PNs in the BLa have been shown to help encode stimuli with negative valence, whereas BLp PNs have been shown to help encode stimuli with positive valence. The mechanisms underlying such coding, however, remain unclear.

Previous studies have shown that the BLA receives dense cholinergic input from the basal forebrain. This suggests acetylcholine (ACh) plays a role in modulating the excitation of BLA PNs and may mediate valence assignment. To understand the anatomical basis for this modulation, the present study used confocal immunofluorescence and retrograde tract-tracing in C57BL/6J mice to examine the distribution of cholinergic input and signaling in the BLA. We employed vesicular ACh transporter (VAChT) antibody to define the distribution of cholinergic axons by labeling cholinergic terminals. VAChT immunoreactivity (ir) was significantly higher in the dorsal BLa than LA or BLp. Linear regression of VAChT-ir across all subdivisions revealed a negative anterior-posterior gradient. To further characterize cholinergic signaling, M1 muscarinic ACh receptors (M1Rs) were immunolabeled. Perikaryal M1R ir was significantly higher in the ventral BLa than BLp. Finally, M1R ir of PNs projecting to the prelimbic (PL) or infralimbic (IL) cortex was evaluated to determine if cholinergic modulation differed according to PN projection target. M1R ir proved to be determined by cell-body location within the BLA rather than projection target. Altogether, these findings indicate cholinergic signaling is biased towards BLa PNs, irrespective of their valence-specific projection targets, to primarily facilitate coding of negative valence for aversive behavioral responses. Supported by the NIMH (R01MH104638 to DDM and AJM) and NIH (GM076277 to JMA).

Speaker

John Amodeo Postbaccalaureate Research Education Program (PREP) Scholar, University of South Carolina School of Medicine

Androgens-Vasopressin intercommunication: a key interaction for social recognition in male mice

Androgens-Vasopressin intercommunication: a key interaction for social recognition in male miceD. Aspesi1, E. Choleris1Department of Psychology and Neuroscience Program, University of Guelph, Guelph, ON, N1G 2W1, CanadaSocial recognition is a pivotal skill for social life in gregarious species, allowing the display of appropriate behaviors towards conspecifics. Several studies highlighted the role of vasopressin (AVP) in regulating social behaviors, including conspecific recognition, social attachment, and parental behavior. The AVP system includes highly sexually differentiated brain regions, such as the bed nucleus of the stria terminalis (BNST) and the lateral septum (LS), which shows more AVP neurons and fibers in males than in females. Androgens are strongly involved in the organization and activation of the AVP circuit. And several studies showed that the interplay between androgens and AVP impact social behaviors, even if the mechanisms involved are currently poorly understood.The aim of this project is to elucidate the rapid, non-genomic, effects of testosterone on AVP neurons in the BNST. Adult castrated male mice, intracerebrally infused with testosterone targeting the BNST, were exposed to a difficult social recognition paradigm. In the difficult version of this test, mice were exposed to a novel mouse after 2 5-minutes sample session with 2 familiar stimuli mice. The investigation ratio (time spent investigating the novel mice/time spent investigating the familiar one) was used as index of social recognition. Preliminary results revealed that infusing testosterone in the BNST facilitates SR, with male CD1 mice spending more time investigating a novel than a familiar castrated mouse. Further investigations will determine the possible mechanisms involved, evaluating the role of testosterone metabolites and the possible modulation of AVP release in the LS.Given that abnormal social behaviors are a main feature of psychopathologies with a strong sex difference such as autism spectrum disorder, pointing out the androgens-AVP interaction could lead to new therapeutic approaches.

Speaker

Dario Aspesi PhD candidate, University of Guelph

Effects of sex and estrous cycle on the expression of oxycodone conditioned place preference in male and female rats.

Effects of sex and estrous cycle on the expression of oxycodone conditioned place preference in male and female rats. Jessica A. Babb 1,2, Nicolas Constantino 4, Mckenzi Hammond 4, Gary B. Kaplan 2,3, Elena H. Chartoff 1,4. 1 Dept. of Psychiatry, Harvard Medical School, 2 Mental Health and Research Services, VA Boston Healthcare System, 3 Depts. of Psychiatry and Pharmacology & Experimental Therapeutics, Boston University School of Medicine, 4 Division of Basic Neuroscience, McLean Hospital, Harvard Medical School. Prescription opioid misuse can escalate to dependence and addiction, and continues to represent a major factor in the ongoing U.S. opioid epidemic. Women report different motivations for initiating drug use and experience different acute and chronic effects of drugs than men. Despite evidence that sex may impact addictive behavior in humans, preclinical rodent models investigating drug-seeking behavior have largely omitted females. In this study, the rewarding properties of the prescription opioid oxycodone were evaluated in adult male and female rats using place conditioning. Adult male and female rats were trained for two days with twice daily conditioning sessions with saline (AM) and 3mg/kg oxycodone (PM). Rats were tested for place preferences before and after conditioning, and a repeated measures ANOVA was used to analyze the effects of sex and estrous cycle on pre- and post-conditioning preference for drug-associated contexts. Male and female rats tested in diestrus similarly showed significant preference for the oxycodone-paired context. However, female rats tested in proestrus and estrus displayed significantly higher conditioned place preference for the oxycodone-paired context than male rats or female rats in diestrus. These data suggest that female sex steroids can influence the rewarding properties of opioids, which could have important consequences for the treatment of opioid use disorder in women. This work was supported by NIH grant R01DA045000 awarded to EHC, VA grant I01RX001144 awarded to GBK, and a VA Interprofessional Polytrauma and Traumatic Brain Injury Rehabilitation Research Fellowship awarded to JAB.

Speaker

Jessica Babb Instructor, Harvard Medical School/VA Boston Healthcare System

Sex-Specific Effects of Ketogenic Diet on Metabolic Outcomes and Stress Response After Pre-exposure to a High-Fat, High- Sugar diet

Sex-specific effects of ketogenic diet on metabolic outcomes and stress response after pre-exposure to a high-fat, high- sugar diet. Brent Bachman, Elizabeth Sahagun, Kimberly P. Kinzig. Purdue University. The continued high rate of overweight and obesity in the United States contributes to the development of diabetes, heart disease, and premature death. To combat obesity and associated diseases, the use of ketogenic diets (KD) is popular. Evidence in support of KD for weight loss and other health conditions exists in the literature, however the association between diet induced ketosis and beneficial effects in males and females remain equivocal. The objectives of this study were to evaluate the relationship between the ketone body beta-hydroxybutyrate and improvements on metabolic parameters in both sexes using a pre-clinical model of obesity. Sprague-Dawley rats were given access to a diet high in fat and sugar (HFS) for 12 weeks. After HFS, animals then switched to either chow (CH) or KD for 4 weeks to model a dietary intervention. The effects of HFS on body weight, adiposity, and stress response were reversed in males that switched to CH (HFS-CH group). These same improvements were observed in females, although impaired glucose tolerance remained. Males that switched to KD (HFS-KD group) showed improvements, however, they still had higher body weight and adiposity than control (CTL). Interestingly, the beneficial effects of KD correlated with plasma BHB levels in females but not in males. These data model effects reported in clinical literature and serve as a valuable translational tool to further test causal mechanisms that lead to desirable outcomes of KD. These sex-specific relationships are particularly important, as KD could potentially affect endocrine mechanisms differently in males and females. Funding source: Purdue Psychology Graduate Student Innovation Award.

Speaker

Brent Bachman Purdue University

Contribution of the Dorsal Medial Striatum to Different Forms of Risk/Reward Decision-Making

Contribution of the Dorsal Medial Striatum to Different Forms of Risk/Reward Decision-Making. Vaishali Bagrodia, Jackson Schumacher, Mieke van Holstein, Hannah LeBouder, Stan Floresco. University of British Columbia.Optimal decision making involving reward uncertainty is integral to adaptive goal directed behaviour. In some instances, these decisions are guided by internal representations of reward history, whereas in other situations, external cues inform a decision maker about how likely a certain choice may yield reward. Several brain regions such as the medial (mPFC) and orbital (OFC) areas of the prefrontal cortex form distributed networks that facilitate different types of risk/reward decision making. The dorsal medial striatum (DMS) receives dense projections from the mPFC and OFC. Furthermore, previous work has shown that the DMS is involved in flexible adaptations to response strategy in set-shifting and reversal learning. However, the contribution of the DMS to risk/reward decision making remains unknown. Thus, this study aims to assess the role of the DMS in different forms of risk/reward decision making. Separate groups of male rats were trained one of two tasks where they had a choice between a small/certain, 1 pellet reward and large/risky 4-pellet reward. In a probabilistic discounting task, reward probabilities changed systematically over blocks of trials (100-6.25% or 6.25-100%), requiring rats to use internal representations of reward history to guide choice. A separate 'œBlackjack' task assessed cue-guided decision-making, where different external auditory cues indicated the 'œodds' associated with the large/risky option (50 or 12.5%). Pharmacological inactivation of the DMS with GABA agonists during the probabilistic discounting task impaired the ability of rats to adapt to the changes in reward probability, resulting in either increases or decreases in risky choice as the odds associated with the large/risky lever decreased or increased over a session. In comparison, DMS inactivation increased risky choices on poor odds trials on the cue-guided Blackjack task. This deficit was also mediated by an inability to adapt their response strategy to the changing reward probabilities. These findings highlight a previously uncharacterized role for the DMS in facilitating flexible action selection during multiple forms of risk/reward decision making.

Speaker

Vaishali Bagrodia Queen Mary University of London

Analysis of gender diversity in IBNS leadership from 2002-2019

Analysis of gender diversity in IBNS leadership from 2002-2019Debra Bangasser1, Gregory Carr2, Amanda Kentner3, & Jared Young41 Temple University, 2 Lieber Institute and Johns Hopkins University School of Medicine, 3 Massachusetts College of Pharmacy and Health Science, 4 University of California, San DiegoAs an organization, the International Behavioral Neuroscience Society (IBNS) encourages research and education in the field of behavioral neuroscience across the globe. Recently, we have created an Ethics & Diversity (E & D) Committee to oversee our commitment to diverse representation across all levels of our Society. One goal of the E & D Committee is to collect and analyze historical data on diverse representation within the Society spanning leadership positions, invited speakers, and award recipients. Here, we present a retrospective analysis of gender diversity in the leadership of the Society from 2002-2019. For this analysis, the roles of President, Secretary, Treasurer, and Council Member were included. The time period was chosen because we had full information on the constituency (Australasia, Canada, Europe, Japan, Latin America, USA, or Students) represented by each Council Member for those years. We counted the total number of people who have served in leadership positions across all roles. We also calculated the number of person-years served for each role because the length of service was not uniform across individuals. A total of 84 individuals served in IBNS leadership from 2002-2019 and 43 (51%) were men and 41 (49%) were women. In terms of person-years, a total of 227 were served and 135 (59%) were served by men and 92 (41%) were served by women. A total of 60 individuals have served as Council Members and 31 (52%) were men and 29 (48%) were women. The person-years split for Council is similar to the overall leadership split with 109 (63%) served by men and 64 (37%) served by women. The gender parity among individuals who served in leadership is encouraging, but there are significant divergences from parity at the level of the individual role and, in the case of Council, constituency represented. These data will be presented in detail at the 2020 poster session. This analysis is the first step in what we expect will be an ongoing effort to monitor the performance of the Society on our goal of having a diverse and inclusive leadership structure.

Speaker

Debra Bangasser Associate Professor of Psychology & Director of the Neuroscience Program in the College of Liberal Arts, Temple University

mTOR inhibitor: A Potential therapeutic strategy targeting PI3K/Akt pathway in type 3 diabetes induced- Neurobehavioral Deficits

mTOR inhibitor: A Potential therapeutic strategy targeting PI3K/Akt pathway in type 3 diabetes induced-Neurobehavioral Deficits Seema Bansal*, Kanwaljit Chopra2, Subodh Kumar1, Madhunika Agrawal 2, Ajay Prakash 1, Bikash Medhi 1Department of Pharmacology1, Post Graduate Institute of Medical Education and Research, ChandigarhPharmacology Research Laboratory2, University Institute of Pharmaceutical Sciences, UGC Center of Advanced Study, Panjab University Chandigarh-160014, IndiaObjectives: The present study was designed with an aim to elucidate the role of mTOR inhibitor (Everolimus) targeting PI3k/Akt pathways in type 3 diabetes induced-neurobehavioral deficits. It is well accepted that PI3k/Akt signaling pathway is a potential therapeutic target through which, various ON/OFF switches of cognitive decline get operated. Methods: Male Wistar rats were administered with intracerbroventricular streptozotocin (3 mg/kg) bilaterally in two divided doses on first and third day, followed by treatment with Everolimus (1 mg/kg; p.o.) for twenty one days. After that, Morris water maze and passive avoidance tests were performed for assessment of memory. Animals were sacrificed to evaluate various biochemical and molecular parameters in brain. To elucidate the mechanism of action, PI3K inhibitor, wortmannin was administered in presence of everolimus in one group. Results: Intracerebroventricular streptozotocin administration results in significant ($p<0.05$) decrease of brain insulin, insulin growth factor-1 levels and alterations in behavioral, biochemical and molecular changes as compared to sham group rats. Treatment with everolimus (1 mg/kg) starting on 3rd day of Streptozotocin administration significantly prevented behavioral, biochemical and molecular changes in type 3 diabetic rats. However, protective effect of everolimus was completely abolished when it was administered in the presence of specific PI-3K inhibitor (wortmannin). Conclusion: Findings from our study reveals that mTOR inhibitor can be an important treatment strategy for the treatment of neurobehavioral deficits occurring due to central insulin dysfunction. Protective effect of these drugs is via PI3K/Akt pathway. Funding Acknowledgement: Funding awarded to Seema Bansal for Postdoctoral fellowship by SERB is highly acknowledgedKeywords: mTOR inhibitor, Type 3 diabetes, Insulin, Inflammation

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Speaker

Seema Bansal Research Associate

Unilateral dopamine denervation in the globus pallidus of rat produces behavioral changes resembling neuropsychiatric symptoms reported in ParkinsonÂ´s patients

Unilateral dopamine denervation in the globus pallidus of rat produces behavioral changes resemblingUnilateral dopamine denervation in the globus pallidus of rat produces behavioral changes resembling neuropsychiatric symptoms reported in Parkinson´s patientsBarón-Quiroz Katia 1,2, Ávila-Velarde Gerardo 1, Chuc-Meza Eliezer 1, García-Ramírez Martha1.1 Escuela Nacional de Ciencias Biológicas IPN, 2 Unidad Profesional Interdisciplinaria de Biotecnología IPN. Parkinson's disease (PD) is a chronic degenerative disease characterized by Motor Symptoms (MS) as hypokinesia, bradykinesia and tremor, and Non Motor Symptoms (NMS) including neuropsychiatric disorders such as mild cognitive impairment, anxiety and depression, which are presented months or years before MS appear. The pathophysiology of NMS is complex and probably includes dopaminergic mechanisms, since bilateral dopamine lesion in the Substantia Nigra pars compacta (SNc) in rat, caused motivational deficits and affective impairments. However, the loss of dopaminergic terminals in the striatum could be not directly related to the anxiety response. Alternatively the external Globus Pallidus (GP) could be implied because is in a key position to influence processing of motor, associative and limbic information and also receives dopaminergic

innervation from SNc. The present work explores the effect of partial dopamine denervation in GP over anxiety, depression, work memory and motor activity in the rat. Dopaminergic lesion in GP was made by unilateral administration in GP with 6-OHDA (500 nL of 6-OHDA, 15 µg/µL). 1 and 5 months after surgery, behavioral tests, were performed. Elevated plus maze (EPM), burying behavior (BB), sucrose preference test (SP), forced swimming test (FST), novel object recognition test (NRT), turning behavior (TB) and spontaneous motor activity (MA). Data were analyzed by one-way ANOVA followed by Student-Newman-Keuls post-hoc analysis. After a month of the surgery there were a significant decrease in time spent in open arms in EPM and increase burying time in BB, both indicative of anxiety. Recognition index was decreased in NRT revealing memory disfunction. There were not effects in SP and FST indicative of depression. Initially turning behavior was only induced by apomorphine administration but after 5 months of surgery the rats showed spontaneous TB and the anxiety and cognitive disfunctions remained. These results suggest that dopamine denervation in GP, could produce behavioral alterations resembling some of the neuropsychiatric symptoms observed in PD patients. neuropsychiatric symptoms reported in Parkinson's patientsBarÃ³n-Quiroz Katia 1,2, Ãvila-Velarde Gerardo 1, Chuc-Meza Eliezer 1, GarcÃa-RamÃrez Martha1.1 Escuela Nacional de Ciencias BiolÃ³gicas IPN, 2 Unidad Profesional Interdisciplinaria de BiotecnologÃa IPN. Parkinson's disease (PD) is a chronic degenerative disease characterized by Motor Symptoms (MS) as hypokinesia, bradykinesia and tremor, and Non Motor Symptoms (NMS) including neuropsychiatric disorders such as mild cognitive impairment, anxiety and depression, which are presented months or years before MS appear. The pathophysiology of NMS is complex and probably includes dopaminergic mechanisms, since bilateral dopamine lesion in the Substantia Nigra pars compacta (SNc) in rat, caused motivational deficits and affective impairments. However, the loss of dopaminergic terminals in the striatum could be not directly related to the anxiety response. Alternatively the external Globus Pallidus (GP) could be implied because is in a key position to influence processing of motor, associative and limbic information and also receives dopaminergic innervation from SNc. The present work explores the effect of partial dopamine denervation in GP over anxiety, depression, work memory and motor activity in the rat. Dopaminergic lesion in GP was made by unilateral administration in GP with 6-OHDA (500 nL of 6-OHDA, 15 Î¼g/Î¼L). 1 and 5 months after surgery, behavioral tests, were performed. Elevated plus maze (EPM), burying behavior (BB), sucrose preference test (SP), forced swimming test (FST), novel object recognition test (NRT), turning behavior (TB) and spontaneous motor activity (MA). Data were analyzed by one-way ANOVA followed by Student-Newman-Keuls post-hoc analysis. After a month of the surgery there were a significant decrease in time spent in open arms in EPM and increase burying time in BB, both indicative of anxiety. Recognition index was decreased in NRT revealing memory disfunction. There were not effects in SP and FST indicative of depression. Initially turning behavior was only induced by apomorphine administration but after 5 months of surgery the rats showed spontaneous TB and the anxiety and cognitive disfunctions remained. These results suggest that dopamine denervation in GP, could produce behavioral alterations resembling some of the neuropsychiatric symptoms observed in PD patients.

Speaker

Katia Barón-Quiroz Químico Farmacéutico Industrial, Instituto Politécnico Nacional, Escuela Nacional de Ciencias Biológicas

Adolescent oxytocin treatment reverses early life stress induced depressive-like outcomes in male and female rats

Adolescent oxytocin treatment reverses early life stress induced depressive-like outcomes in male and female rats. Thornton, Jade; Everett, Nicholas; Webb, Paige; Turner, Anita; Cornish, Jennifer; Baracz, Sarah. Macquarie University, NSW, Australia. Exposure to early life stress (ELS) is associated with an increased vulnerability for mental health disorders later in life, including depression. Despite this known link, there are no approved pharmacotherapies to protect against the emergence of psychiatric disorders after ELS. Recent preclinical work has shown that treatment with the neuropeptide oxytocin (OT) in adulthood reduces depression-like behaviours in male rats with a history of ELS. However, it is unknown whether OT treatment during adolescence, a crucial developmental window for the OT system, can prevent depression-like behaviours after ELS in both males and females. Thus, this study aimed to determine whether chronic OT administration during adolescence can ameliorate the long-term effects of ELS on depression-like behaviours in both sexes. Long Evans pups underwent maternal separation (MS) for either 15 or 360 minutes on postnatal days (PND) 1 to 21. During adolescence (PND 28-42), rats received a daily intraperitoneal injection of either OT (1mg/kg) or saline. In adulthood (PND 57 onwards), anhedonia was measured using an effortful choice paradigm, where rats could work for highly palatable sucrose pellets, or

consume the less rewarding but easily available rat chow. Learned helplessness was measured using the forced swim test by examining the time spent immobile. The spleen, thymus, and adrenal glands were then weighed due to their involvement in immune and endocrine system functions that can be impacted by ELS. We found that in both sexes, MS increased learned helplessness, but had no impact on anhedonia. Importantly, both males and females exposed to MS who received adolescent OT injections displayed a reduction in learned helplessness to a level consistent with non-separated controls. Additionally, MS reduced spleen weight in males, and thymus weight increased in OT treated control males. For females, MS increased adrenal gland weight, which was reduced by adolescent OT administration. Altogether, this suggests that an adolescent OT treatment schedule is capable of preventing the emergence of depression-like symptoms in both sexes, and adrenal hypertrophy in females, who have experienced ELS. This work was funded by Macquarie University.

Speaker

Sarah Baracz Lecturer, Macquarie University

The influence of perinatal environmental enrichment on offspring rodents' anxiety- and depressive-like behavior: A scoping review

The influence of perinatal environmental enrichment on offspring rodents' anxiety- and depressive-like behavior: A scoping reviewKheana Barbeaua, Kayla Boileaua, Jessica E Sparlinga, Anne TM Konklea,b,caSchool of Psychology, University of Ottawa, Ottawa, Ontario, CanadabInterdisciplinary School of Health Sciences, University of Ottawa, Ottawa, Ontario, CanadacUniversity of Ottawa Brain and Mind Research Institute, Ottawa, Ontario, CanadaEvidence indicates that environmental enrichment (EE) can alter biological and behavioral markers of depression and anxiety. Favorable effects of EE are thought to be more pronounced if it is delivered during a sensitive developmental period, when stress and behavioral response systems are maturing and developing. Current literature report mixed findings on the effects of EE on offspring rodents' anxiety- and depressive-like behavior, which may be due to methodological variation in EE protocols or behavioral measurement of anxiety and depressive-like behavior. For these reasons, a scoping review was employed to examine the literature regarding the effects of various types of EE on these behaviors in rodent offspring. Relevant key terms were searched across five databases, and articles published within the past ten years were screened against inclusion and exclusion criteria. Included articles (N = 35) were thematically analyzed. Results suggest that more articles have examined the impact of EE on offspring anxiety-like behavior (n = 23) than on depressive-like behavior (n = 12). Overall, results yielded mixed findings; however, there was a trend toward decreased anxiety- and depressive-like behaviors in enriched offspring rodents. Results highlight the impact of EE on decreasing anxiety- and depressive-like behavior in offspring rodents and the implications of methodological variation, such as type of EE administered, timing of EE, behavioral tests used, and species of rodents, on favorable outcomes of EE.No source of funding.

Speaker

Kheana Barbeau PhD Candidate Experimental Psychology, University of Ottawa

Mesenchymal Stromal Cells Protect the Blood-Brain Barrier, Reduce Astrogliosis, and Prevent Cognitive and Behavioural Impairments in Experimental Sepsis

Mesenchymal stromal cells protect the blood-brain barrier, reduce astrogliosis, and prevent cognitive and behavioural impairments in experimental sepsisBarbosa-Silva, Maria C1; Silva, Adriano YO1; Amorim, Erica A1; Lima, Maiara N1; Oliveira, Helena A1; Granja DVM, Marcelo G1; Fagundes, Paula M1;Campos, Raquel MP2;Rocco, Patricia RM2; Castro-Faria-Neto, Hugo C1; Maron-Gutierrez, Tatiana11-Oswaldo Cruz Institute-Fiocruz 2- Institute of Biophysics- Federal University of Rio de JaneiroSepsis is a systemic inflammatory host-response against a pathogen; it is the largest cause of admission to intensive care units (ICUs) in the United

States. Sepsis-associated encephalopathies (SAEs) are neurological complications that occur during or after sepsis events. SAE causes long-term neurological consequences affecting memory, cognition and mood. Currently, there is no prevention or treatment for neurological damage resulting from SAEs. Thus, investigating new therapies is necessary. Both clinical and experimental studies have been show the effects of cell therapy in neurodegenerative diseases. Indeed, the immunomodulatory capacity of mesenchymal stromal cells (MSCs) is well established. The aim of the present study was to evaluate the effects of MSC therapy on blood-brain barrier (BBB) maintenance, astrocyte activation, cognitive and behavioural damage in an experimental model of sepsis. In order to investigate that, we used male adult Swiss mice and cecal ligation and puncture (CLP) surgery for sepsis induction and sham-operated animals were used as control. Six hours after surgery, mice were treated with MSC intravenously (1Ã—105 cells in 0.05 mL of saline/mouse) or saline. MSC therapy led to a reduction in systemic levels of IL-1Î², IL-6, and MCP-1, a decrease in cortical and hippocampal cytokine levels, a reduction in astrogliosis (evaluated by immunofluorescence) and BBB protection (evaluated by Evans Blue Dye Assay). These results might be associated with an improvement in spatial memory (Morris Water Maze test), aversive memory (fear-conditioned test) and anxiety-like behavior (Elevated plus maze test). Thus, we can conclude that a single dose- therapy with MSC led to an improvement in cognitive damage, behavioural impairments, protection of the BBB, reduction in local levels of cytokines and astrogliosis and these effects might be associated with a decrease in systemic levels of inflammatory mediators. Funding resources: Faperj, CNPq and CAPES

Speaker

Maria Carolina Barbosa-Silva IOC-fiocruz-Brazil

Specific steroid hormone involvement in dorsal hippocampal D2-type dopamine receptor mediated social learning

Specific steroid hormone involvement in dorsal hippocampal D2-type dopamine receptor mediated social learning. Noah Bass 1,2, Elena Choleris 1,2, Maura Hickey 1,2. University of Guelph 1,2,3. Social learning is one of the most common forms of learning and can be defined as learning that occurs via social interaction and/or observation. In animals, social learning may be tested using the social transmission of food preference (STFP) paradigm. Recent findings revealed that dorsal hippocampal (HPC) infusions of a D2-type dopamine (DA) receptor antagonist blocked social learning in gonadally intact female mice but not males, suggesting a role of sex hormones in DA facilitated social learning. Later, we showed that dorsal HPC infusions of the same D2-type DA receptor antagonist blocked social learning in gonadectomized male and female mice but not their gonadally intact counterparts. These findings suggest a direct interaction between dorsal HPC D2-type DA receptors and sex hormones in modulation of social learning in mice. Estrogens regulate many forms of cognition in the female and male brain including social interactions and social learning. In males this may be done through the biosynthesis of androgens to estrogens via aromatization. What is still unknown are the specific sex hormone(s) involved in HPC D2-type DA receptor regulated social learning. We began by investigating the DA-sex hormone interaction in social learning in male mice. By utilizing a typical STFP paradigm, castrated (CAS) 'œobserver' (OBS) mice received slow releasing sex hormone implants of estradiol or a sesame oil control in experiment 1, or dihydrotestosterone (DHT; potent androgen) or a cholesterol control in experiment 2. OBS received bilateral dorsal HPC infusions of the D2-type DA receptor antagonist raclopride (20 Âµg/ÂµL) 10-minutes prior to a 30-minute social interaction with a recently-fed, same-sex, familiar 'œdemonstrator' (DEM). The OBS then underwent an 8-hour choice test where they had free access to two novel flavored food diets, one of which their respective DEM consumed prior to their social interaction. If social learning occurs, the OBS will prefer the DEM diet. It is hypothesized that the beneficial effects of circulating androgens in social learning are driven by estrogenic mechanisms in male mice. It is predicted that HPC infusions of raclopride will block the STFP in CAS mice treated with sesame oil and DHT, but not in mice treated with estradiol. Funded by NSERC.

Speaker

Noah Bass University of Guelph

A novel non-toxic histone deacetylase inhibitor enhances spatial memory consolidation in male mice

A novel non-toxic histone deacetylase inhibitor enhances spatial memory consolidation in male mice. Sarah Beamish 1, Jawad Belayet 2, Towheed Rahman 2, Samer Alanani 3, Douglas Steeber 3, Mahmun Hossain 2, Karyn Frick 1. 1 Department of Psychology, 2 Chemistry & Biochemistry, 3 Biological Sciences at the University of Wisconsin-Milwaukee, Milwaukee WI, 53211. Memory dysfunction is a hallmark of Alzheimer's disease (AD), yet truly effective treatments for memory loss do not exist. Memory dysfunction stems in part from reduced gene expression that leads to decreased levels of proteins essential for neural plasticity. Gene expression is facilitated by histone acetylation, an epigenetic mechanism that regulates chromatin accessibility. Compounds that maintain histone acetylation, called histone deacetylase inhibitors (HDACi), enhance memory by preventing deacetylation of core histone proteins, thus promoting a transcriptionally active state. Although HDACi are promising therapeutics that could be used to prevent or delay memory loss associated with AD, existing HDACi have poor solubility and undesirable toxicity. To address these shortcomings, our group has developed a novel HDACi compound, MJM-1, that is brain-penetrant and shows no evidence of toxicity. Here, we determine the extent to which MJM-1 can enhance spatial and object recognition memory in male mice using the object placement (OP) and object recognition (OR) tasks, respectively. During testing, one training object was moved to a new location in the open field (OP task) or was replaced with a novel object (OR task). Mice received a post-training intraperitoneal (i.p.) injection of either negative control (100% DMSO), positive HDACi control (sodium butyrate; 0.6 g/kg NaBu), or one of three doses of MJM-1 (20, 30, or 40 Âµg/g). Mice receiving NaBu, 20 Âµg/g MJM-1, or 40 Âµg/g MJM-1 spent significantly more time with the moved object, whereas DMSO-treated controls mice did not, suggesting that the established HDACi NaBu and two doses of the novel HDACi MJM-1 enhanced spatial memory consolidation. Mice receiving the 30 Âµg/g dose of MJM-1 also tended to prefer the moved object. Conversely, MJM-1 did not affect object recognition memory. Thus, the novel non-toxic brain penetrant HDACi MJM-1 can enhance spatial memory consolidation, suggesting encouraging proof of principle for future testing in models of aging and AD. This work is funded by the UWM Research Foundation Catalyst Grant Program.

Speaker

Sarah Beamish University of Wisconsin-Milwaukee

Age and Sex Impact Ethanol Sensitivity & Socialization in DBA/2J mice

Age and Sex Impact Ethanol Sensitivity & Socialization in DBA/2J mice. M.A.M. Bent1, A.C. Pais1, E. Blay1, and J.T. Wolstenholme1.1. Virginia Commonwealth University, Richmond, VA, 23284, USA. Adolescence is a critical developmental period characterized by increased socialization and drug experimentation. Alcohol is a commonly abused drug during adolescence which may lead to lasting alterations in behavior and ethanol sensitivity. Adolescents have shown to be differently impacted by alcohol than adults. This study assessed immediate and persistent changes in ethanol sensitivity and social interaction following binge ethanol exposure in adolescence and adulthood. We hypothesized that binge ethanol would cause reduced sedation in adolescent animals, while adults would show be increased sedation. While social interaction would be negatively impacted by ethanol in both age groups & timepoints. In experiment 1, adolescent male & female mice were administered, via oral gavage, 4 g/kg ethanol or water intermittently from PND 29-42. After behavioral tests were conducted for social interaction at PND 43 & 63/64, and LORR at PND 52/54 and 74/75. In experiment 2, adult male & female mice underwent the same dosing procedure as experiment 1 from PND 68-81, social interaction was tested at PND 77 & 97, and LORR was measured at PND 84 & 110. LORR duration was significantly decreased due to sex & age with females and adolescent animals showing decreased duration at both timepoints. LORR onset was not altered at the 3 week timepoint for both cohorts or 24-hour timepoint in adults but showed a sex effect in adolescent mice with males showing increased onset than females. When comparing cohorts, a three-way ANOVA showed age & sex significantly decreased duration at both timepoints and onset at 3 weeks post ethanol binge. The social interaction test revealed that within the adolescent cohort, performance was not altered at either testing timepoint, while adult mice with a history of ethanol increased duration in the corners. A three-way ANOVA

showed age significantly impacted duration in the interaction zone with adults spending less time interacting than adolescents at both timepoints. Conversely, adults spent more time in the corner zones than adolescents and this was impacted by sex, age, & treatment. This study suggests developmental age and sex significantly &differentially affect the response to acute ethanol and socialization. Supported by NIAAA R01AA026347 to JTW.

Speaker

Maria Alexis Bent Neuroscience Graduate Student, Virginia Commonwealth University

Social behavior and communication in a full Ube3a deletion rat model

Social behavior and communication in a full Ube3a deletion rat model. Elizabeth Berg 1, Stela Petkova 1, Yutian Shen 1, Timothy Fenton 1, Anne Anderson 2, Scott Dindot 3, Kevin Nash 4, Edwin Weeber 4, Jacob Ellegood 5, David Segal 6, Markus WÃ¶hr 7,8 Jill Silverman 1. 1 MIND Institute, University of California Davis School of Medicine, 2 Baylor College of Medicine, 3 College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, 4 University of South Florida, 5 Toronto Centre for Phenogenomics, The Hospital for Sick Children, 6 University of California Davis, 7 Philipps-University of Marburg, 8 University of Southern Denmark. Angelman Syndrome (AS) is a rare neurodevelopmental disorder is characterized by developmental delay, intellectual disabilities, impaired receptive and expressive communication skills, motor and balance deficits, and often a happy, excitable demeanor with frequent laughter. The genetic cause of AS is the loss of expression of UBE3A (ubiquitin-protein ligase E6-AP) in the brain, typically due to a deletion of the maternal 15q11-q13 region. Previous studies have been performed using a mouse model with a deletion of a single exon of Ube3a. Since three splice variants of Ube3a exist, this has led to a lack of consistent reports and the theory that perhaps not all mouse studies were assessing the effects of an absence of all functional Ube3a. Herein, we report the characterization of social communication phenotypes in the full Ube3a deletion rat model of Angelman Syndrome. We discovered that Ube3am-/p+ rats exhibited aberrant social interaction and communication, behavioral deficits which were large in effect size, easily apparent in the larger rodent species, and detected using tasks that are unique to rats. While Ube3am-/p+ rats displayed normal pro-social motivation to release a trapped conspecific, they exhibited reduced initiation of species-typical play behaviors and abnormally elevated emission of pro-social 50-kHz juvenile 'œlaughter' vocalizations. Our report identifies, for the first time, unique and robust AS-relevant social communication phenotypes useful as preclinical outcomes to test various strategies for gene and molecular therapies for AS. This work was supported by FAST Grant Award #A18-0382 (Silverman, PI).

Speaker

Liz Berg Graduate Student Researcher, MIND Institute, UC Davis School of Medicine

The Angelman syndrome in a rat model: Pharmacological treatment with the growth factor IGF-II in the 50-kHz playback paradigm

The Angelman syndrome in a rat model: Pharmacological treatment with the growth factor IGF-II in the 50-kHz playback paradigm. Berz, Annuska C. 1, Berg, Elizabeth L. 2, Silverman, Jill L. 2. 1 Philipps-University Marburg, Germany, 2 Univ. of California Davis Sch. of Med., Sacramento, CA. The Angelman syndrome (AS) is a rare neurodevelopmental disorder typically caused by loss of UBE3A (ubiquitin-protein ligase E6-AP) expression in the brain. Patients amongst others exhibit a happy demeanor, cognitive impairments and deficits in communication, which are central to the human phenotype. In our newly developed rat model for AS, animals carry a knockout of the Ube3a gene on the maternal allele in the chromosomal region 15q13-15. Because rats emit ultrasonic vocalizations (USVs) of different frequencies for communication purposes, our rat model represents a suitable tool to study the communicational deficits of AS. The so-called 50-kHz USVs represent a positive affective state and are commonly referred to as '˜rat-laughter'. To test the signal features of those USVs, our lab uses playback of these calls on a radial maze. While the

presentation of 50-kHz USVs evokes rats to socially approach to the source of sound, whereas a second presentation several days later does not. This habituation phenomenon occurs due to a social acoustic memory. In this study, knockout rats with a maternally inherited deficiency of Ube3a (m-/p+) showed a reduced social approach response to 50-kHz USV playback. When repeating the 50-kHz USV playback, knockout animals also exhibited an altered approach behavior compared to littermate controls. A prominent sex difference was found in regards to the habituation phenomenon, which suggests a failure to form a social acoustic memory in females. The insulin-like growth factor II (IGF-II) has been shown to enhance learning and memory in mouse models for autism. To test whether a social deficit in approach behavior during the repeated playback paradigm can be rescued, we injected Ube3a m-/p+ and littermate control rats with IGF-II. Preliminary results give evidence that deficits in forming a social acoustic memory can be rescued in female Ube3a m-/+ rats via IGF-II treatment. This experiment is not only the first one where repeated playback was tested in a genetically modified rat model, but it is also of major importance for future studies to develop potential therapeutical approaches for AS. Funded by the DFG, the G. A. Lienert-Stiftung.

Speaker

Annuska Berz PhD candidate, Philipps-University Marburg

Extinction effectiveness: finding the influencing factors

Extinction effectiveness: finding the influencing factors. Besseling, Amber 1, Hengerer, Bastian 2, Cahill, Emma N. 3, 1 Vrije Universiteit Amsterdam, 2 Boehringer Ingelheim Pharma, 3 University of Cambridge. Extinction learning to reduce fearful associations is not guaranteed to be effective. Two suggested reasons for extinction failure are a change in salience of the threat cue and individual variation. Using fear-conditioning, we set out to uncover the behavioural influences of altering threat cue volume in rats at memory test and during extinction. Furthermore, we categorised rats according to well-established measures of fear and anxiety, freezing and ultrasonic vocalisations respectively, to investigate the use of individual variances as predictors for extinction effectiveness. The results suggested that a change in salience influences fear retrieval but not extinction. Moreover, categorisation by hypervigilance (excessive freezing compared to conspecifics) and sustained fear (relative freezing after the conditioned stimulus has ended) did not predict fear extinction behaviour, whereas vocalisations differentially predicted extinction learning, depending on the salience used. Despite the lack of an effect of change in salience, hypervigilance, and sustained fear in extinction learning, we suspect that the consolidation of extinction memory may be affected and therefore suggest that future studies consider this. This was work was funded by Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany.

Speaker

Amber Besseling Master intern, University of Cambridge

An exploration of probiotic treatment and restricted postpartum resources on varying immune and threat responses in male and female Long-Evans rats.

An exploration of probiotic treatment and restricted postpartum resources on varying immune and threat responses in male and female Long-Evans rats. Bhalerao, J1; Kent, M2; Bowen, G1; Jackson, E1; Meisel, E1; Ploppert, E1; Jacob, J1; Lambert, K1. 1 University of Richmond; 2 VMI. Restricted nesting and bedding has been shown to alter maternal responsiveness resulting in negative impacts on offspring. The current study investigated the effects of probiotics on animals exposed to early life stress (ELS; i.e., restricted nesting and bedding materials during the postpartum period) or standard postpartum conditions on various anxiety and immune functions in male and female rats (n= 6/group). On PND 23, pup play and social behaviors were assessed for three days (5 min/day). A significant interaction between sex and resources indicated that social grooming was lower in the restricted group males with no differences observed in the females;

further, a significant interaction indicated that females had higher levels of self-grooming in the standard resource group with the males exhibiting less in the low resource group. On the third day, increased play bouts were seen in the low resource groups. On PND 28, pups were given probiotics (lactobacilli; 10^9 CFU/ml H2O) or milk protein for 6 weeks. During an open field test (OFT), the low resource group traveled a greater distance whereas the standard resource group exhibited longer durations of movement. Further, when the OFT was modified to include predator odor and a hide, a probiotic treatment x resources interaction indicated that in standard resource animals, the probiotic rats exhibited less freezing behavior and low resource rats treated with vehicle rats exhibited fewer bouts of freezing. Further, a sex x treatment interaction indicated probiotic treated males excreted the most fecal boluses with no in the vehicle treated animals. Wound healing was assessed by administering a 3mm dermal punch to the dorsal scapular area of each animal. Latency to heal showed a significant 3-way interaction; specifically, in the low resource animals, probiotic treated males had the slowest rate of healing whereas no effects of sex or probiotic were observed in the standard resource group. Adrenal weights taken at the time of perfusion showed surprising results of lower adrenal weights in the low resource group. The results suggest that probiotic intervention differentially affects males and females exposed to resource related ELS.

Speaker

Janhavi Bhalerao University of Richmond

Rodent sex and age differences in locomotor and anxiety-like behaviours: From adolescence to adulthood

Rodent sex and age differences in locomotor and anxiety-like behaviours: From adolescence to adulthood. Indra R. Bishnoi1,2, Klaus-Peter Ossenkopp1,2, Martin Kavaliers1,2. 1 Graduate Program in Neuroscience, Western University, London, Ontario, Canada, 2 Department of Psychology, Western University, London, Ontario, Canada.Risk-taking behaviors are a primary contributor to elevated adolescent injury and mortality. Locomotor and anxiety-like behaviors in rodents have been used to examine risk-taking. Here, we examined risk-taking behavior (i.e. changes in locomotor and anxiety-like behaviors) from early to late adolescence and adulthood in male and female rats in the open-field (OF) apparatus and the light-dark (LD) test. We also examined whether these behaviors are affected by an early adolescent immune stressor, lipopolysaccharide (LPS). Long-Evans male and female rats were injected with LPS (200 ug/kg) or vehicle control in early adolescence (postnatal day [PND] 30 and 32). Anxiety-like behavior and locomotor activity were measured in early (PND 38 '‟ 40), late adolescence (PND 50), and adulthood (PND 88 and 98) in the OF and in early adolescence (PND 42) and adulthood (PND 90) in the LD test. Early and late adolescent rats displayed significantly greater locomotor and anxiety-like behaviors than adult rats in the OF and LD. Sex differences were also found, with adolescent and adult females displayed greater locomotor and anxiety-like behaviors than male rats in the OF and LD test. LPS administered twice in early adolescence did not have a significant impact on either locomotor or anxiety-like behaviors.This work was funded by Natural Sciences and Engineering Research Council of Canada (NSERC) grants awarded to M. Kavaliers and K.-P Ossenkopp. I.R. Bishnoi was supported by the NSERC Canada Graduate Scholarship-Master's and Canada Graduate Scholarship-Doctoral Program scholarships.

Speaker

Indra Bishnoi Doctoral Student, Western University

Cotinine and 6-hydroxy-L-nicotine improves neurobehavioral changes and reduce oxidative stress in a zebrafish (Danio rerio) model of Alzheimer's Disease

Cotinine and 6-hydroxy-L-nicotine improves neurobehavioral changes and reduce oxidative stress in a zebrafish (Danio rerio) model of Alzheimer's DiseaseR.S. Boiangiu 1, M. Mihasan 1, L. Hritcu 11 Department of Biology, Alexandru Ioan Cuza University of IasiThe most common form of dementia, Alzheimer's Disease

(AD), is a progressive neurodegenerative disorder characterized, among others, by cognitive decline, mood changes and loss of forebrain cholinergic neurons. Zebrafish (Danio rerio) is emerging as an increasingly successful model for translational research on human neurological disorders and has been successfully used to simulate AD pathology. The presence of nicotinic acetylcholine receptors (nAChRs) in the cholinergic neurons suggests their involvement in memory, learning, and cognition. Nicotine is an exogenous agonist of nAChRs and was shown to improve memory, attention, and learning. However, its therapeutic use in AD was limited by cardiovascular and addictive side-effects. Here, we aim to investigate the effects of two structural related nicotine derivatives, cotinine (COT) and 6-hydroxy-L-nicotine (6HLN), on memory deficits, anxiety and oxidative stress in a zebrafish model of AD induced by scopolamine (SCOP). Doses of 1 and 2 mg/L of COT and 6HLN were administered acutely by immersion to zebrafish after SCOP (100 ÂµM) treatment. Memory performances and anxious behavior were assessed using in vivo tasks such as Y-maze and novel object recognition test (NOR) and novel tank diving test (NTT) respectively. Also, we evaluated the impact of COT and 6HLN on oxidative stress by measuring the level of reduced glutathione (GSH) and carbonylated proteins. In this study, we have shown that 6HLN and COT improve memory in Y-maze and NOR tasks and reduced the anxious behavior in NTT. Moreover, these nicotinic derivatives increased the content of GSH and decreased the level of carbonylated proteins, suggesting that COT and 6HLN reduce the oxidative stress in SCOP-treated zebrafish. Our results demonstrate that COT and 6HLN promote brain antioxidant action and mitigate scopolamine-induced anxiety and memory deficits in zebrafish. These findings suggest that COT and 6HLN could be used as neuropharmacological agents in AD. This work was co-funded by the European Social Fund, through Operational Programme Human Capital 2014-2020, project number POCU/380/6/13/123623, project title<>.

Speaker

Razvan Boiangiu PhD student, Research Assistant, Alexandru Ioan Cuza University of Iasi

Aggressive behavior in female Syrian hamsters results in an increase in both AMPA and metabotropic glutamate receptor expression in the nucleus accumbens

Aggressive behavior in female Syrian hamsters results in an increase in both AMPA and metabotropic glutamate receptor expression in the nucleus accumbens. Borland, Johnathan 1, Swanson, Sam 1, Kim, Ellen 1, Rothwell, Patrick 1, Mermelstein, Paul 1, Meisel, Robert 1. 1 Department of Neuroscience, University of Minnesota. There is strong support for the rewarding properties of aggressive behaviors to be critical for the expression and development of adaptive social relationships. It potentially both buffers stress and protects from the development of psychiatric disorders. However, due to the false belief that aggression is not a part of the normal repertoire of social behaviors displayed by females, almost nothing is known about the neural mechanisms mediating the rewarding properties of aggression in half the population. In the following study, using hamsters as a well-validated and translational model of female aggression, we investigated the effects of aggressive experience on the expression of markers of postsynaptic structure (PSD-95, Caskin I) and excitatory synaptic transmission (GluA1, GluA2, GluA4, NR2A, NR2B, mGluR1a and mGluR5) in the nucleus accumbens, caudate putamen and prefrontal cortex. Aggressive experience resulted in an increase in PSD-95, GluA1 and the dimer form of mGluR5 24 hours following aggressive experience. There was also an increase in the dimer form of mGluR1a 1 week following aggressive experience. Aggressive experience also resulted in an increase in the strength of the association between these postsynaptic proteins and glutamate receptors, supporting a common mechanism of action. In addition, one week following aggressive experience there was a positive correlation between the monomer form of mGluR5 and multiple AMPAR and NMDAR subunits that was not observed in females that did not have aggressive experience. In conclusion, we provide evidence that aggressive experience in females results in an increase in the expression of postsynaptic density, AMPARs and group I metabotropic glutamate receptors, and an increase in the strength of the association between postsynaptic proteins and glutamate receptors. This suggests that aggressive experience may result in an increase in excitatory synaptic transmission in the nucleus accumbens, potentially encoding the rewarding and behavioral effects of aggressive interactions. Research was supported by NSF IOS 1856724 to R.M. and J.B. was supported under NIDA award T32DA007234 to P.M.

Speaker

Johnathan Borland Postdoctoral Research Associate, University of Minnesota

Executive control deficits after neurodevelopmental insult: New theraputic approaches.

Executive control deficits in neurodevelopmental disorders: New therapeutic approaches. Jonathan L. Brigman 1,2, Sarah Olguin 1, Jayapriya Chandrasekaran 1,2, Johnny Kenton1. 1 Department of , Neurosciences, University of New Mexico School of Medicine. 2 New Mexico Alcohol Research Center, UNM Health Sciences Center. Growing evidence demonstrates the negative effects moderate alcohol consumption during pregnancy has on executive function. We have recently shown that moderate prenatal alcohol exposure (PAE) increases perseverative responding on a touchscreen-based visual reversal learning task. Utilizing in vivo electrophysiology, we found that single unit and local field potential activity during behavior are significantly altered in the orbitofrontal cortex (OFC) and dorsal striatum during early reversal. Importantly, these alterations were concurrent with decreases in the synchronous activity between the OFC and dorsal striatum. First, we trained PAE and SAC mice through discrimination and then expressed channelrhodopsin in the OFC and fitted fiber stubs targeting the cortex. After 4 weeks of expression, PAE and SAC mice re-attained discrimination criteria and were then tested on the reversal. Light pulses following a correct choice delivered during early reversal was sufficient to reduce perseveration in PAE mice compared to non-stimulated controls. Next, we utilized the same exposure to show that PAE spared acquisition and extinction of an instrumental response, but significantly increased reinstatement responses. We then showed that increased maternal care via a communal nest rescued these effects. Finally, we utilized EEG recording to investigate the effects of this moderate exposure on attention and cognitive control. PAE mice showed similar acquisition of target responding on a five choice serial reaction time task. However, when nontarget trials were added during a five choice continuous performance task, PAE mice had significantly increased false alarms and reduced sensitivity index. These changes were accompanied by alterations in parietal and frontal EEG signals seen in control mice. Together, these studies elucidate how the cortex, is functionally altered by exposure to alcohol in utero, leading to long term impairments in executive function that can be rescued by direct circuit manipulations or early life environment. Supported by National Institute on Alcohol Abuse and Alcoholism grants: 1R01AA025652-01, 1P50AA022534-01 & T32AA014127

Speaker

Jonathan Brigman Associate Professor & Regents' Lecturer, University of New Mexico SOM

Epigenetic regulation of histone marks may underlie adolescent binge ethanol induced memory deficits

Epigenetic regulation of histone marks may underlie adolescent binge ethanol induced memory deficits. Emily Brocato1, Rachel Stevenson1, Jennifer Wolstenholme1. 1 Virginia Commonwealth University. The prefrontal cortex (PFC) undergoes significant changes during adolescence, including synaptic pruning and myelination. Due to the ongoing development of PFC structure and connectivity, alcohol exposure during this time is particularly damaging. Consuming alcohol, especially in binges, has been shown to negatively impact the adolescent brain, resulting in brain structural changes, decreased myelin, and deficits in attention and memory. Specifically, memory deficits that lasted into adulthood were seen in a novel object recognition task, three weeks after the last dose of ethanol. Recently, our lab measured gene expression changes in the PFC to uncover the mechanisms by which ethanol induces these changes, and results showed that adolescent binge ethanol decreased myelin-related gene expression as well as the expression of chromatin remodeling genes responsible for the methylation of histone 3 lysine 9 (H3K9). H3K9me3 is a repressive histone mark that results in transcriptional silence, and is needed for the differentiation of oligodendrocyte progenitor cells to mature oligodendrocytes. Specifically, H3K9me3 must be present at certain synaptic transmission-related genes, to repress gene expression and allow oligodendrocyte differentiation to occur. Ethanol-induced dysregulation of H3K9me3 could result in decreased oligodendrocyte differentiation, leading to deficits in PFC myelin, which could ultimately underlie the persistent memory deficits of adolescents exposed to binge ethanol. To investigate this potential

mechanism, binge levels of ethanol (4g/kg) or water were administered to adolescent mice. Twenty-four hours after the last dose of ethanol, molecular analyses including chromatin precipitation coupled to qPCR, and qPCR for myelin and synaptic transmission related gene expression were performed to further investigate the link between ethanol-induced H3K9 dysregulation and myelin deficits. In a separate cohort, the novel object recognition task was tested in adulthood, three weeks after the last dose of ethanol. Here, I discuss how our lab is taking steps to understand how this epigenetic mechanism may underlie persistent memory deficits associated with adolescent binge ethanol. Supported by NIAAA R01AA026347 to JTW.

Speaker

Emily Brocato Graduate student, Virginia Commonwealth University

Cannabis Indica decreases willingness to exert cognitive effort in male rats

Hannah Brodie1, Brett Hathaway1, Andrew Li1, Matthew Hill2, Catharine Winstanley11University of British Columbia 2University of Calgary Despite cannabis being one of the most widely used recreational drugs, chronic use has been associated with numerous psychosocial deficits, potentially mediated by drug-induced cognitive impairments. The main psychoactive compound, Î”9-Tetrahydrocannabinol (THC), has been identified as the cannabinoid responsible for such cognitive impairments. Acute THC administration has been shown to decrease willingness to exert cognitive effort, yet little is known about the chronic effects of THC on cognitive effort. There are two types of cannabis plant strains broadly categorized as 'œSativa' and 'œIndica'. It is unclear if these two strains have different effects on cognition despite their morphological differences and varying prevalence of terpenes and terpenoids, which are chemical compounds thought to mediate the effects of THC. In this study, we tested the hypothesis that Sativa and Indica THC extracts would impair cognitive processes, namely the willingness to exert more cognitive effort in return for larger rewards. Male Long-Evans rats (N = 32) performing the rodent Cognitive Effort Task received varying oral doses of acute and chronic Sativa and Indica THC oil. Rats chose between two options differing in the cognitive effort required to complete the task and the magnitude of reward delivered. We found that a large acute dose of Indica THC oil decreased the number of high-effort high-reward trials completed, without impairing accuracy. In contrast, the same acute dose of Sativa THC oil did not affect choice. Furthermore, a low chronic dose of Indica or Sativa oil did not influence choice. These results suggest that Indica but not Sativa THC administered orally impairs decision-making involving cognitive effort. These findings thus reveal potential dissimilarities in the way different cannabis strains affect cognition.This research was funded by grants from NSERC and CIHR.

Speaker

Hannah Brodie Graduate Student, University of British Columbia

Effects of manipulating PFC-NAC subcircuit activity on methamphetamine use in B6 mice.

Effects of manipulating PFC-NAC subcircuit activity on methamphetamine use in B6 mice. Brown, Chelsea 1; Beltran, Jacqueline 1; Yen, Waylon 1; Tran, Tori 1; Barger, Brooke 1; Williams, Nyssa 1; Park, Asher 1; Kippin, Tod 1; Szumlinski, Karen 11 University of California, Santa BarbaraPrior research on the neurobiology of methamphetamine (MA) use has primarily probed the effects of high MA doses that model late-stage addiction. Not so well characterized are the neurological changes during early stages of drug use that may help to explain individual variation in vulnerability to MA addiction and/or the transition from recreational use to addiction. The long-term neuroplasticity underlying changes over time to dose-dependent subjective MA effects has been strongly associated with glutamate signaling, particularly the glutamatergic projection from the prefrontal cortex (PFC) to the nucleus accumbens (NAC). Sub-circuits of this projection travel from the prelimbic (PL) PFC, which is thought to drive reinforced behaviors, to the core of the NAC, which is thought to contribute to decision-making by encoding the motivational value of expected goals, and the shell of the NAC, which is known for updating reward saliency following new experiences. Activity of these

sub-circuits were manipulated bidirectionally using a dual virus chemogenetic approach called Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). A retrograde adeno-associated viral vector (AAV) carrying Cre was infused into the NAC core or shell, and then an AAV carrying either a Cre-dependent excitatory DREADD, Cre-dependent inhibitory DREADD, or mCherry control was infused into the PL, ensuring that only neurons projecting from the PL to the core or shell would express the DREADDs or mCherry. Operant conditioning procedures were utilized to assess the effects of these manipulations on the acquisition of MA use in male B6 mice. Activating the PL-shell sub-circuit significantly reduced the number of mice that reached acquisition criteria, as well as the amount of active responses, during the acquisition phase, compared to the control or inhibitory viral infusions. Manipulating the PL-core sub-circuit revealed no statistically significant effect of the viral infusions. These results may indicate that the NAC shell sub-region is more involved with MA acquisition, which reflects its role in updating decision making with new experiences. The core may be more responsible for guiding decision-making following drug experience, which should be explored in future studies probing the effects of manipulating its sub-circuits on the behavior of drug-experienced mice.

Speaker

Chelsea Brown PhD Candidate, University of California, Santa Barbara

Sex differences in measures of "apathy-like behaviour" in the 3xTG-AD mouse model of Alzheimer's Disease

Sex differences in measures of "apathy-like behaviour" in the 3xTG-AD mouse model of Alzheimer's DiseaseAuthors: Richard E. Brown(1), Emre Fertan(1), Aimee A. Wong(1), and Fuat Balci(2) Authors' affiliations: (1)Dalhousie University, Halifax, NS, Canada (2) Koc University, Istanbul, TurkeyResearch: Alzheimer's disease (AD) is the most common cause of dementia and apathy is one of the most common behavioural symptoms of AD. Apathy-like behaviour has been reported as a reduction in voluntary activity in the 3xTg-AD mouse model. Here we examine deficits in goal-directed motivated behaviour in 3xTg-AD mice as measures of apathy. We tested male and female 3xTg-AD mice and their B6129S/F2 wildtype (WT) controls between 4 and 13 months of age in the Hebb-Williams maze (HWM) and in a peak interval timing task. The HWM is a visuo-spatial learning task with varying levels of difficulty in which mice are motivated with food reward. Both working memory and long-term memory can be assessed. In order to evaluate the age related changes in cognitive decline in the 3xTg-AD mice, we tested 4 and 7 month old male and female, as well as 13 month old female 3xTg-AD and WT control mice. We found that the 3xTg-AD mice performed worse than the WT mice in the working memory phase but better in the long-term memory test. Female mice of both genotypes performed worse than males in the long-term memory test. Moreover, the female mice often failed to eat the food reward and the test performance had a significant negative correlation with this behaviour, suggesting that apathy rather than cognitive deficit was causing poor performance in this task. In the interval timing performance task, we tested 10 month old mice in a 9-hole (using one hole) operant box for sucrose reward. While the interval timing ability of male and female 3xTg-AD mice did not differ from WT controls, there was a significant sex difference in measures reflecting motivational state as female mice of both genotypes initiated anticipatory responding later in the trial and had lower response amplitudes than males, suggesting that interval timing deficits were due to decreased reward motivation of the female mice. Both of the studies above have identified apathy as the reason of poor performance for the female 3xTg-AD and WT control mice in reward based cognitive tasks, which shows the importance of measuring motivation for reward in cognitive tasks as it may act as a confounding variable masking or appearing as cognitive deficits. Funding: This research was funded by an NSERC of Canada Research Grant to REB.

Speaker

Richard Brown Manager, Dalhousie University

Age and Injury Induce Asymmetries in PDE11A4 Trafficking

Age and injury induce asymmetries in PDE11A4 trafficking.Sophie Bruckmeier1, Nicole Gorny1, Latarsha Porcher1, Fabiola Placeres-Uray2, Coleen M. Atkins2, Michy P. Kelly11.Department of Physiology, Pharmacology, and Neuroscience, University of South Carolina School of Medicine2.Department of Neurological Surgery, The Miami Project to Cure Paralysis, University of Miami Miller School of MedicineThe brain, especially the hippocampus (HIPP), exhibits molecular and morphological hemispheric asymmetries both in the context of regular function and disease/injury. Our lab studies the function of an enzyme that is almost exclusively expressed in the HIPP, phosphodiesterase 11A (PDE11A). PDE11A degrades cyclic nucleotides (cAMP and cGMP), but it is not yet known if it may contribute to hippocampal asymmetries. We have found that PDE11A mRNA expression increases with age in the human HIPP and is further elevated in aged individuals with a history of traumatic brain injury (TBI) and dementia vs individuals with TBI but no dementia. In mice, we see PDE11A protein expression also increases with age and ectopically accumulates in filamentous 'œstructures' resembling axons, chiefly in the ventral subiculum (VS). Here, we aim to determine if ectopic PDE11A accumulation occurs asymmetrically following injury or aging. First, young adult male C57BL6/J (C57) mice received moderate controlled cortical impact over the right parietal cortex (TBI) or a craniotomy only (sham). 3 months after surgery, TBI mice expressed higher levels of PDE11A in the VHIPP relative to sham mice. The TBI and sham surgery formed numerous PDE11A structures in the VS (TBI>Sham), with more present in the left vs right VS of both groups. We then compared PDE11A expression in young vs aged C57 female mice. Aged mice showed increased PDE11A protein expression in the HIPP, with significantly more PDE11A structures in the left vs right VS. To determine if these asymmetries are driven by high PDE11A expression levels or if they are specifically driven by age or injury, we examined PDE11A structures in young male BALB/cJ mice as they express much higher levels of PDE11A vs C57s. Young BALB/cJ mice showed an equal number of PDE11A structures in the left vs. right VS. Together, these data suggest that the PDE11A asymmetries observed in injured and aged mice are not simply driven by higher PDE11A protein expression, but rather by some other mechanism as yet to be determined.Grant Support: NIA Grant R01AG061200

Speaker

Sophie Bruckmeier University of South Carolina School of Medicine

Antagonistic effects of dopamine-dependent positive emotional arousal system and acetylcholine-dependent aversive emotional arousal system in the rat brain as studied by emission of ultrasonic calls.

Antagonistic effects of dopamine-dependent positive emotional arousal system and acetylcholine-dependent aversive emotional arousal system in the rat brain as studied by emission of ultrasonic calls. Brudzynski, Stefan M; Silkstone, Michael, Department of Psychology, Brock University, St. Catharines, Ontario, L2S 3A1, Canada. It has been established that two ascending reticular systems are responsible for emotional arousal, which is separate from the cognitive arousal. The activity of the ascending dopaminergic system is causing appetitive (positive) emotional arousal while the activity of the ascending cholinergic system is causing aversive (negative) emotional arousal. We have postulated that these two arousal systems are functionally antagonistic as measured by emission of relevant calls. The goal of this experiment was to pharmacologically induce the positive arousal by injection of apomorphine into the rat medial shell of the nucleus accumbens and then verify, whether or not, the subsequent pharmacological initiation of an aversive arousal by intracerebral injection of carbachol into the anterior hypothalamic/preoptic region or septum will be affected by the preceding injection. It was hypothesized that the aversive arousal initiated by the subsequent injection would be reduced or abolished by the initial positive arousal. The results confirmed this prediction. Initial intraaccumbens injection of D1/D2 dopamine receptor agonist, apomorphine (3 µg) significantly decreased ($p< 0.01$) the subsequent aversive response signaled by emission of 22 kHz ultrasonic vocalizations, which were induced by intrahypothalamic-preoptic injection of carbachol (1µg). This reducing effect was obtained only by injection of apomorphine into the centro-medial portion of the shell of the nucleus accumbens. Similarly, intraaccumbens injection of apomorphine (3 µg) significantly decreased ($p< 0.04$) the subsequent aversive response signaled by emission of 22 kHz ultrasonic calls induced by injection of carbachol (1µg) into the lateral septum. The results confirmed the hypothesis that appetitive and aversive arousals mediated by the cholinergic or dopaminergic systems, respectively, are in an antagonistic relationship. Supported by research grant from NSERC of Canada.

Speaker

Stefan Brudzynski Professor, Brock University

Phosphodiesterases PDE2A and PDE10A both change mRNA expression in the human brain with age, but only PDE2A changes in a region-specific manner with psychiatric disease

Phosphodiesterases PDE2A and PDE10A both change mRNA expression in the human brain with age, but only PDE2A changes in a region-specific manner with psychiatric disease. Burbano, Steven; Farmer, Reagan; Kelly, Michy. University of South Carolina; University of South Carolina School of Medicine; University of South Carolina School of Medicine. Studies have linked altered cyclic nucleotide signaling in the pathophysiology of major depressive disorder (MDD), bipolar disorder (BPD), and schizophrenia (SCZ), thus we explored how phosphodiesterases 2A (PDE2A) and 10A (PDE10A) may change in brains of these patients. With the use of autoradiographic in situ hybridization on postmortem brain tissue obtained from the Stanly Foundation Neuropathology Consortium, we measured expression of PDE2A and PDE10A mRNA in brain regions involved in psychiatric pathophysiology, including cingulate cortex, orbital frontal cortex, superior temporal gyrus, hippocampus, parahippocampal cortex, amygdala, and the striatum. Through the Allen Institute for Brain Science Brainspan database, we also assessed how PDE2A and PDE10A expression changes in these regions across development. Compared to controls, all patients showed reduced PDE2A mRNA in the amygdala. However, PDE2A expression changes in frontal cortical regions were only significant in patients with SCZ, while those in caudal entorhinal cortex, hippocampus, and striatum were most distinct in patients with BPD. PDE10A expression was only detected in striatum and did not vary by diseases; however, all groups had significantly less PDE10A mRNA expression in ventral versus dorsal striatum. Across development, PDE2A mRNA increased in these regions whereas PDE10A mRNA expression decreased in all regions except striatum. Thus, PDE2A mRNA expression changes in both a disorder- and brain region-specific manner, linking PDE2A as a novel diagnostic and/or therapeutic target. These are the acknowledgements: The authors would like to thank the subjects and their families for donating tissue as well as the Stanley Foundation and Dr. Maree Webster for overseeing tissue collection. The authors would also like to acknowledge Tyler McKenzie for technical support. This work was funded by start-up funds from the USC School of Medicine (MPK), a Magellan Scholar Award and mini-Grant from the USC Office of the Vice President for Research (RF), and a grant from NIMH (1R01MH101130 to MPK).

Speaker

Steven Burbano Undergraduate Research Assistant, University of South Carolina School of Medicine

Identifying Depression in Rodents using Ultrasonic Vocalization and Behavioural Analyses

Identifying Depression in Rodents using Ultrasonic Vocalization and Behavioural AnalysesCandace Burke1, Madison Mauro1, Lily Aleksandrova2, Anthony Phillips2, Sergio M. Pellis1, David R. Euston11Dept of Neuroscience, Univ. of Lethbridge, Lethbridge, AB, Canada2 Department of Psychiatry, University of British Columbia, Vancouver, BC, CanadaThe Wistar-Kyoto (WKY) rat was developed as a control for the spontaneous hypertensive rat but has subsequently also been used as a genetic animal model of depression due to its hyper-responsiveness to stress. We used anticipation of social reward (i.e., a play partner) to assess behavioural and vocal differences between the WKY and normal Wistar (WI) rats in the juvenile period. We found marked differences between groups; the WKY rats, were less active, vocalized less, and used significantly less types of 50-kHz calls in comparison to their WI counterparts. In adulthood the same differences existed in overall activity, types of vocalizations and the behavioural vocal profiles used by the two groups of animals. These findings provide a robust baseline for an animal model of depression using a social paradigm. A paradigm amenable for using WKY rats to evaluate the efficacy of pharmaceutical interventions as potential treatments of depression.Supported by NSERC and Alberta Innovates Health Solutions.

Speaker

Candace Burke PhD student , University of Lethbridge

The role of prefrontal circuits in odor-directed attention

The role of prefrontal circuits in odor-directed attention.Hillary Cansler 1,2, Estelle in '˜t Zandt 1,2, & Daniel Wesson 1,2.1 Department of Pharmacology and Therapeutics, University of Florida. 2 Center for Smell and Taste, University of Florida. Decades of research has characterized the ways in which the brain alters sensory processing based upon internal cognitive states like attention. While these questions have been thoroughly investigated in the visual system, similar investigation of the olfactory system, where the underlying circuitry is vastly different, is in its relative infancy. Recent work from our lab showed that single unit odor representations in the olfactory tubercle (OT) exhibit increased signal-to-noise during selective attention to odors, in a similar manner to what is observed in other sensory cortices. Still, the underlying mechanisms of this phenomenon in the olfactory system, where thalamic processing between the periphery and the sensory cortex is absent, are not known. Here, we aimed to investigate one intriguing candidate mechanism: the direct pathway between the medial prefrontal cortex (mPFC) and the OT. We first characterized this pathway using retrograde AAV tracing, which revealed that neurons in layer 5 of the prelimbic (PrL) and infralimbic (IL) cortices target the OT. Next, we injected anterograde AAVs encoding synaptophysin tagged with either GFP or mRuby into the PrL and IL, respectively, in the same rat to determine the specific regions within the OT that are targeted by these mPFC subregions. We found that the mPFC preferentially targets layers 2 and 3 of the anteromedial OT. Notably, mPFC innervation of the OT is much denser than innervation of the piriform cortex, another primary olfactory cortex. To investigate the potential functional significance of this pathway, we simultaneously recorded local field potentials in the olfactory bulb, mPFC, and OT while rats engaged in a task that requires selective attention to odors. This approach allows us to examine networks dynamics within and between each of these structures, which may reveal candidate mechanisms by which odor-evoked activity in the OT is modulated by attention.This work was supported by the following funding sources: NIDCD F32DC018232 to HC, NIDCD R01DC014443 to DW, and NIDCD R01DC016519 to DW.

Speaker

Hillary Cansler Postdoctoral Fellow, University of Florida

Behavioral Effects of an Opioid Overdose and Naloxone Rescue

Behavioral effects of an opioid overdose and naloxone rescue. Hanna Carmon, Shannon M. Thompson, Matthew S. McMurray. Miami University, Miami University, Miami University. The opioid epidemic has become a growing issue throughout the United States. In the year 2016, synthetic opioids such as fentanyl were among the most common drugs involved in overdose deaths. Fentanyl induces a hypoxic state during an overdose, in which the brain becomes deprived of oxygen and can be damaged. Overdose rescue via naloxone is relatively new and prevents opioids from binding to opioid receptors, saving an overdosing individual. Thus, recent individuals who have overdosed on opioids are more likely to survive due to the increased use of naloxone; however, the consequences of overdose-induced brain damage are unknown. The purpose of this study is to determine the neurobehavioral effects of a fentanyl overdose and naloxone recovery on decision-making. This potential effect could explain reports of increased likelihood of relapse following overdose. To do this, a novel rat model was first developed that accurately depicts the timing and extent of physiological events that occur when an individual overdoses on fentanyl. This model was then used to compare the effects of an overdose and naloxone recovery to naloxone alone on decision making through a behavioral flexibility task: probabilistic reversal learning. Results showed significant dose-dependent respiratory and cardiac suppression during an overdose, but no significant impairment in reversal learning after animals received an overdose and rescue. Therefore, impairments following overdose and rescue may be restricted to other cognitive domains, such as impulse control or emotional

regulation. Future studies will determine if such effects are present, and identify the location and extent of neural damage caused by overdose and rescue. Funding: Undergraduate Summer Scholars Award, Miami University, Hanna Carmon; Undergraduate Research Award, Miami University, Hanna Carmon; Pilot Grant, Miami University, Matthew McMurray; Pilot Grant, Tufts University.

Speaker

Hanna Carmon Undergraduate Researcher, Miami University

Inflammatory signaling transmission between sick pups and their dams

Inflammatory signaling transmission between sick pups and their damsSilvia Castany1, Anders Blomqvist2, Kiseko Shionoya2, David Engblom1,21 Center for Social and Affective Neuroscience, Department of Clinical and Experimental Medicine, Linkoping University.2 Division of Neurobiology, Department of Clinical and Experimental Medicine, Linkoping University.Parents are a natural source of help during childhood. An extensive literature on maternal buffering has demonstrated that many kinds of stressors affecting the offspring, such inflammation, can be buffered by maternal presence and care. However, sustained psychological distress, such as having a sick child, can have a negative impact on the parent's health increasing their risk of developing mental illnesses such as anxiety and depression. So far, few studies have addressed the behavioral and physiological consequences of having sick offspring in the postpartum period. The aim of this study is to study how immune challenged infants can signal their parents and elicit changes in their behavior and stress levels. We used a mice model of maternal interaction in which mouse pups are given an immune challenge (LPS i.p.) and the molecular and behavioural consequences taking place in the dams (mother) are studied. We found that inflammation in the pups resulted in a robust activation of the HPA axis and inflammatory gene expression in the brain of the dams., This is surprising given the fact that the dams did not receive any injection of LPS. Moreover, dams exposed to sick pups showed increased nursing behavior and increased time in the nest during along the experimental period. We also studied whether the physical contact may be relevant for this transmitted inflammatory phenomenon. We still saw an induction of inflammatory signaling in the hypothalamus of the dam when we physically separated them, although it was weaker compared to the induction seen when the pups and the dams were close to each other. These findings highlight the importance of mother-infant interactions in early-life inflammation states providing new insights on the events taking place on the parents with chronically sick kids.

Speaker

Silvia Castany Quintana Postdoctoral researcher, University of Linkoping

Identifying the metabolomic signature of a psychiatric disease: The right tool for the job

Identifying the metabolomic signature of a psychiatric disease: The right tool for the job

Lauren Chaby 1, Heather Lasseter 1, Andrew Thompson 1, Timothy Vaughan 1, Lee Lancashire 1, Magali Haas 1, Andreas Jeromin 11 Cohen Veterans Bioscience Inc., New York, NY

Metabolomics can be a powerful tool for understanding complex disease mechanisms. Yet, metabolomic analyses vary widely in metabolite coverage, robustness, and throughput, and it is unclear how to leverage metabolomics to optimize identification of the metabolic signature of psychopathologies such as posttraumatic stress disorder (PTSD). We conducted a systematic review of metabolomics efforts in PTSD to structure an evaluation of technical performance and dynamic range of metabolomics platforms. The current metabolomics study is part of larger efforts towards cross-platform comparisons across modalities to enable large-scale biomarker discovery and replication, led by the RAPID-Dx initiative to discover and

replicate biomarkers in PTSD, with an inflammatory biomarker assay evaluation previously completed. Here, clinical and healthy control plasma as well as technical standards were utilized for comparisons across metabolomics platforms. Coverage and performance were mapped for metabolites implicated in PTSD through (i) case-control studies and (ii) protein-encoding genes identified with genome-wide association studies (GWAS) in PTSD. Our systematic review revealed that efforts in PTSD have largely relied on discovery-based approaches. Findings varied across techniques but emphasized essential and long chain fatty acids. Of identified metabolites, platform coverage ranged from 25-80%. For metabolites associated with GWAS loci, e.g. PARK2, coverage varied from 5-90%. Technical performance varied across workflows; for example, coefficients of variation (CV%) within assays for duplicate PTSD samples ranged from 0.4 - 76.1%. Analyses across platforms have yet to replicate metabolites associated with PTSD, although there is overlap in metabolite classes. The current study enables identification of the best fit-for-purpose platform to determine the metabolomic signature of a clinical state using technical performance and coverage. Recommendations beyond PTSD can be generated using the publicly available metabolomics database generated by the current study.

This work was supported by Cohen Veterans Bioscience (CVB) and generous grants COH-0013 and COH-0003 from Steven A. Cohen for the RAPID-Dx program.

Speaker

Lauren Chaby Senior Scientific Program Manager, Cohen Veterans Bioscience

Reduced cognitive flexibility following chronic voluntary alcohol intake may be recovered following abstinence.

Reduced cognitive flexibility following chronic voluntary alcohol intake may be recovered following abstinence. Charlton, AJ 1,2; Geerlofs, L 1,3; Lawrence, AJ 1,2; Perry, CJ 1,2. 1 Florey Institute of Neuroscience and Mental Health, Australia, 2 University of Melbourne, Australia, 3 Hogeschool Utrecht University of Applied Sciences, Netherlands. Relapse poses a major barrier to treating alcohol use disorder (AUD). Interestingly, cognitive function, impaired in AUD, also predicts relapse likelihood following rehabilitation. Despite this, little research has questioned whether the cognitive decline accompanying AUD can be recovered. Physical exercise has neuroprotective and restorative effects following an acute alcohol insult, though the effect on chronic alcohol intake is unknown. This research examines the cognitive effects of chronic alcohol consumption, and whether changes incurred are recoverable with abstinence and physical exercise. Rats voluntarily consumed alcohol over 6 months (15% ethanol). Based on consumption, they were categorised as high drinkers of alcohol (greater than 4.5g/kg/24 hours) or low drinker controls (less than 4.5g/kg/24 hours). Rats then undertook cognitive tasks using touchscreen chambers where they acquired visual discrimination between two stimuli, and then had these contingencies reversed (reversal learning) - a measure of cognitive flexibility. Rats were tested following no abstinence, or after four weeks abstinence, with or without voluntary running wheel exercise. With no abstinence, high drinkers showed a deficit in reversal learning compared to low drinkers, performing fewer trials with fewer correct. Importantly, there was a positive correlation between alcohol intake (g/kg) and days to acquire reversal learning, suggesting a dose-sensitive deficit. Following abstinence, and regardless of exercise condition, there were no significant differences in performance between the high and low alcohol drinkers, suggesting that the deficit in reversal learning was recovered. By recapitulating key deficits of alcohol use disorder in humans, these results provide evidence that recovery is possible, which has important clinical implications for treatment. Ongoing studies hope to elucidate the mechanism driving this recovery. Acknowledgements: This research is supported by an Ian Scott PhD scholarship from Rotary Health Australia awarded to AJC and an NHMRC-ARC Dementia Research Development Fellowship APP1107144 awarded to CJP.

Speaker

Annai Charlton PhD Candidate, Florey Institute of Neuroscience and Mental Health

Performance is not enough: using transitional probabilities for a better understanding of rodent behaviour in a non-aversive operant box paradigm

Performance is not enough: using transitional probabilities for a better understanding of rodent behaviour in a non-aversive operant box paradigm. Charron,Valerie, Talbot,Joey, Plamondon,Helene. School of Psychology Department of Neuroscience University of Ottawa. Transitional probabilities are part of sequential analysis and can be defined as a predicted likelihood that one behaviour might be followed by another, be it from the same type or a different one (O'Connor, 1999). It is an easy computerized way to predict the onset of many behaviours, a setting that is not currently offered in commonly used statistical software such as SPSS. In 1999, O'Connor proposed a script that can easily be modified and add in SPSS' syntax mode, allowing for easy sequential analysis data. While this paper was published twenty-one years ago, only around 50 studies were published using this technique since. The objective of this study is to illustrate how transitional probabilities can be a useful tool to highlight the richness of behaviours in rodent studies. Twenty adolescent rats were divided in a trained and an untrained group and randomly assigned an actor or observer role. In a double operant box divided by a clear wall, the actor rat had access to two levers, an easy press one giving a sucrose pellet to itself and a harder press one, giving a reward to itself and the observer rat in the other compartment. Rats in the trained group first underwent a pretraining session, in which only the actor rats were accustomed to the levers. Performance (i.e. number presses on both levers) and transitional probabilities (coded with Boris coding software and analyzed using the O'Connor method) were compared. Transitional probabilities were used to assess which behaviours were linked together and the likelihood of which one would follow the initial behaviour (e.g. There's an 'œX %' chance that behaviour 'œA' will be followed by behaviour 'œB'). A one-way MANOVA revealed that rats from the trained group pressed more on the hard lever (M=227.06, ÏƒxÌ… =17.95) than untrained rats (M=.53 ÏƒxÌ… =14.66, p< .001) but not on the easy lever (M=303.38, ÏƒxÌ… =37.42, M=269.93 ÏƒxÌ… =45.83, p= .911, respectively). The transitional probabilities revealed that trained rats had more interactions and a better understanding of the task than the untrained group. While performance is useful to assess the rat's ability to execute specific tasks, it's a limited tool in terms of behavioural analysis. Transitional probabilities are a relevant and easy method to include in behavioural studies to further understand data in animal research.

Speaker

Valerie Charron PhD Student, University of Ottawa

Learning impairments in the adenosine A1 receptor (A1R) knock-out mouse

Learning impairments in the adenosine A1 receptor (A1R) knock-out mouseChasse, Renee 1, 2, Malyshev, Alexey 3, Vega, Gabriel 1, 2, Volgushev, Maxim 1, 2, Fitch, R. Holly 1, 21. University of Connecticut Dept. of Psychological Sciences, Behavioral Neuroscience Division, Storrs, CT 06269.2. CT Institute for Behavioral and Brain Sciences, University of Connecticut, Storrs, CT, 06269.3. Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, Russia 117485.Dynamics of learning are complex, spanning changes in behavior to modifications in regional synaptic function. Most approaches to learning research focus on one or two levels, for example concurrent behavioral and neuroimaging study, or concurrent EEG and neuroimaging. The current study attempts to link changes at the behavioral level directly to synaptic physiology and function. We specifically assess a novel preparation with deletion of the Adenosine 1 receptor gene, typing previously reported anomalies in synaptic plasticity to behavioral learning measures in mice engineered for a knock-out of the A1R gene. Prior research has specifically demonstrated that a blockade of A1R by an antagonist lead to decreased weight-dependent synaptic plasticity, but it remains unclear what this means for systemic behavioral function (and particularly learning). The goal of this experiment was to phenotype the A1R deletion by evaluating putative visual discrimination learning deficits specific to a systemic A1R deletion in a mouse model, together with concurrent slice physiology in primary visual cortex. Results reveal an elegant parallel between robust deficits in complex pairwise visual discrimination (but not a simple visual learning task), along with concurrent confirmation of adenosine-related changes in synaptic transmission from these same animals. Possible mechanisms linking altered synaptic function and behavioral learning will be discussed.Supported by an award from the University of Connecticut Research Excellence program to MV and RHF, funding from the CT Institute for Behavioral and Brain Sciences (IBACS), and the UConn Murine Behavioral Neurogenetics Facility (MBNF).

Speaker

Renee Chasse Graduate Student, University of Connecticut

Sex-modulated Norepinephrine Function in Mediating Exploration-exploitation Tradeoff

Sex-modulated Norepinephrine Function in Mediating Exploration-exploitation Tradeoff Chen, C. S1., Ebitz, R. B.2, Bindas, S.1, Knep, E.1, Grissom, N11Department of Psychology, 2Department of Neuroscience, University of Minnesota, MNIn an uncertain world, we balance two goals: exploiting rewarding options and exploring potential better alternatives. Often, there are a range of individual solutions to this dilemma, but we know little about the neural bases of the interindividual variability in the exploration-exploitation trade-off. One major axis of interindividual variability in decision-making is sex. Sex is a profound modulator of the locus coeruleus-norepinephrine (LC-NE) system that has long been thought to underpin exploration. However, it remains unclear how the balance between exploration and exploitation differs across sexes, much less the role of LC-NE in these sex differences. Here, we compared male and female mice in a restless two-arm bandit task, which encourages constant shifting between exploration and exploitation. The reward probabilities of two arms changed independently and stochastically over trials so that the animals could only infer values through sampling and integrating choice-outcome history. We found that that females were more likely to repeat behaviors that produced reward. Fitting reinforcement learning models revealed that the learning rate of females was higher than males and, unexpectedly, increased over time, suggesting that females 'œlearned to learn'. To determine whether increased learning in the females was due to LC-NE tone, we systemically administered propranolol, a Î²-adrenergic receptor antagonist. Surprisingly, this did not reduce the learning rate in females, but instead increased the stickiness of choices and reduced decision noise. Together, these results highlight sex differences in solving the explore/exploit dilemma differently and a novel role of LC-NE system in regulating exploration via regulating behavioral stickiness, rather than learning rate.

Speaker

Cathy Chen Graduate student, University of Minnesota

Establishing a Drosophila behavioral model for pathogenic gene/drug screening of hyperactivity and distraction behaviors by computer vision method

Establishing a Drosophila behavioral model for pathogenic gene/drug screening of hyperactivity and distraction behaviors by computer vision methodAuthors:Chen, Ching-Hsin 1(Presenting Author); Yang, Chi-Lien 2; Juang, You-Zan 3; Chiang, Ann-Shyn 2,4,5,6,7,8; Tsai, Hung-Yin 1,4.Authors' Affiliations:1Department of Power Mechanical Engineering, National Tsing Hua University, Hsinchu 30013, Taiwan2Institute of Systems Neuroscience, National Tsing Hua University, Hsinchu 30013, Taiwan 3Department of Life Science, National Tsing Hua University, Hsinchu 30013, Taiwan4Brain Research Center, National Tsing Hua University, Hsinchu 30013, Taiwan5Institute of Physics, Academia Sinica, Taipei 11529, Taiwan 6Department of Biomedical Science and Environmental Biology, Kaohsiung Medical University, Kaohsiung 80780, Taiwan7Institute of Molecular and Genomic Medicine, National Health Research Institutes, Zhunan, Miaoli 35053, Taiwan8Kavli Institute for Brain and Mind, University of California at San Diego, La Jolla, CA 92093-0526, USAResearch:Establishing a behavioral model is important for screening potential pathogenic genes and drugs. By introducing Drosophila melanogaster that shares 75% pathogenic genes with human, we present a machine vision system that help to distinguish the effects of genes or drugs to behaviors by monitoring locomotion and social behaviors of 20 fruit flies in a 50 mm Ã— 50 mm arena. In this study, the tool we proposed can determine hyperactivity and distraction behaviors from fruit flies by 3 behavioral indexes: hyperactivity, impulsivity and interactive attention indexes. We found besides genetic mutations, the genetic background also plays an important role in behaviors of fruit flies. Our results proved this system can provide details of behaviors with high tracking accuracy (99.4%), which can be a potential tool for large scale screening for pathogenic genes and drugs.Funding Acknowledgement:We are sincerely

grateful for Bloomington Stock Center to provide us fly stocks. Also this work was supported by Higher Education Sprout Project and research projects [grant nos. 105-2628-E-007-002-MY3, 106-2811-E-007-031, 107-2923-E-007-004] funded by the Ministry of Science and Technology and Ministry of Education in Taiwan.

Speaker

Ching Hsin Chen PhD candidate, National Tsing Hua University

High-throughput behavioral screening of synthetic cathinones in larval zebrafish (Danio Rerio)

High-throughput behavioral screening of synthetic cathinones in larval zebrafish (Danio Rerio)Yu Chen1, Raghad A. Elhag1, Alexander S. Wisner1, Austin C. Horton2, Frederick E. Williams1, Isaac T. Schiefer2, F. Scott Hall1 Department of Pharmacology and Experimental Therapeutics1, and Medicinal and Biological Chemistry2, College of Pharmacy and Pharmaceutical Sciences, University of Toledo College of Pharmacy, Toledo, Ohio, USABackground: The use of synthetic psychoactive cathinones (SPCs) has increased over last two decades and poses substantial public health concerns. Although SPCs are structurally related to amphetamines, variations in pharmacology has been reported as compared to traditional amphetamines. Clinical studies showed that the use of synthetic cathinones is often associated with changes in motor function including agitation, tremor, and hyperkinetic and stereotypical movements, in addition to other cognitive and physiological symptoms. There are currently more than 150 synthetic cathinones identified. Given the vast number of these substances, a high throughput approach is needed to systematically evaluate their pharmacological properties. To this end, we used 5 days-post-fertilization (dpf) zebrafish to assess the behavioral effects of synthetic cathinones. This initial report focuses on the methylone series of synthetic cathinones. Methods: behavioral effects of synthetic cathinones were examined in 5pdf zebrafish larvae in a 96 well-plate format. Methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA) were also examined for comparison. METH, MDMA, methylone, ethylone, or butylone (1ÂµM ~ 10mM) were administered by direct immersion to 5dpf zebrafish. Behavior endpoints including distance moved, velocity, thigmotaxis, and mobility state were then measured using DanioVision (Noldus) under alternative light/dark cycles for 1hr. Results: Baseline mobility was significantly influenced by lighting conditions. Larval zebrafish were more active in dark periods. All drugs tested produced a monophasic, hypolocomotive effect and the highest concentration tested produced complete immobility in larval zebrafish. Locomotor stimulant effects were not seen with SPCs, but these were not seen with METH either, likely do to ceiling effects, consistent with previous observations in zebrafish Conclusion: Our data provides the first evidence of behavioral effects of SPCs in larval zebrafish. In contrast to behavioral studies in mammals, SPCs, METH and MDMA do not produce stimulant effects in zebrafish larvae. Continuing work will examine the behavioral effects of other SPCs. Funding: NIH DA045350 (FSH)

Speaker

Yu Chen University of Toledo

The Cognitive Effects of Dopaminergic Lesions to Anterior Cingulate Cortex in Rats

The cognitive effects of dopaminergic lesions to anterior cingulate cortex in rats. M. K. Clement 1, C. S. Pimentel 1, J.A. McGaughy 1. 1 University of New Hampshire, Durham, NH USA. Dysfunction in the anterior cingulate cortex (ACC) has been implicated in many neuropsychiatric disorders such as, but not limited to, attention deficit hyperactivity disorder, addiction, and schizophrenia. Dopaminergic projections to the ACC are hypothesized to be critical to error processing, timing of responses, and filtering irrelevant information. In previous work, rats with excitotoxic lesions to the ACC showed an increased susceptibility to distraction when a complex stimulus contained an attribute previously paired with reinforcement, but, were not more distractible than sham lesioned subjects when presented with irrelevant stimuli that did not have a reinforcement history. The current study is aimed at identifying the neurochemical basis of these effects.

Rats infused with a selective dopaminergic toxin or it's vehicle into the ACC were assessed in two attentional tasks, an attentional set shifting task (ASST), and a sustained attention task (SAT). The ASST measures the ability of subjects to form and shift an attentional set in the presence of irrelevant cues that have previously been paired with reinforcement. The SAT includes tests of distractors never predictive of reinforcement, changes in timing of events as well as timing between responses and reinforcement. Both male and female dopaminergic lesioned subjects were more susceptible to distraction and impaired when reinforcement contingencies were reversed in the ASST. Dopamine lesioned rats were not susceptible to distraction when irrelevant stimuli had no prior reinforcement history. Dopaminergic lesions impaired, but did not abolish, the ability of subjects to adapt when the timing of responses and reinforcement was changed. Female, but not male, lesioned rats were impaired when the event rate was made more temporally unpredictable. Together these data show that DA in the ACC is involved in filtering salient stimuli and updating responding when reinforcement contingencies are altered. In females, but not in males, this system is also critical to alter responding when task events become more temporally unpredictable. Acknowledgements: Funding provided by the Cole Fund.

Speaker

Madison Clement UNH

5xFAD mice do not exhibit translational sleep or seizure pathology commonly associated with Alzheimerâ€™s disease

5xFAD mice do not exhibit translational sleep or seizure pathology commonly associated with Alzheimer's diseaseCope Zackary A; Sukoff Rizzo, Stacey JUniversity of Pittsburgh Department of Medicine Aging InstituteOn average, humans are living longer, healthier lives than ever before and our global population continues to climb. As life expectancy estimates from the World Health Organization top 72 years, age related disease incidence is expected to rise commensurately, making Alzheimer's disease (AD) one of the most pressing public health challenges in a generation. To date, model mice utilized in the study of AD have focused on well characterized mutations in genes coding for amyloid precursor protein (APP) and presinilin (PSEN), which induce heavy plaque burden and neuron loss leading to early onset AD. The 5x familial AD (5xFAD, B6.Cg-Tg (APPSwFlLon,PSEN1*M146L*L286V) 6799Vas/Mmjax; JR# 34848) mouse carries five human transgenes encoding 3 mutant forms of APP (Swedish, Florida, London) and 2 of PSEN (M146L, L286V) and has been widely used in the study of AD due to heavy beta-amyloid (AÎ²) deposition, gliosis, and neuron loss. Though, pathology is detectable in young adult mice, weakening translational value. Further, these mutations lead to familial early-onset AD, which only represents 2-3% of all AD cases. These experiments sought to use telemetric electroencephalography (EEG) to determine if 5xFAD mice on a congenic C57BL/6J background exhibit two biomarkers relevant to AD: absence seizure-like spike wave discharge (SWD) and sleep pathology. As validation, SWDs were characterized in C3H (n=4) mice exhibiting frequent seizures. C3H mice exhibited SWD elevated in frequency relative to C57BL/6J (n=4) controls. By comparison, no interaction (F(1, 12)=0.32, p=0.58) or effect of genotype (F(1,12)=2.22, p=0.16) was detected in SWD in 11 month old 5xFAD mice relative to age- and sex- matched C57BL/6J controls. No differences in sleep stage distribution were detected in 5xFAD mice compared to controls (F(3, 36)=0.013, p=0.99) with typical circadian patterns evident in both groups over 72 hours. Results indicate 5xFAD mice do not exhibit AD related sleep or seizure activity, questioning their relevance to AD beyond a model for plaque deposition and related comorbidities. This highlights a critical need for mice reflecting polygenic and environmental interactions with age contributing to AD, a primary goal of the Model Organism Development for the Evaluation of Late Onset AD (MODEL-AD) consortium. Future studies will focus on aged mouse models with sporadic risk alleles being created by MODEL-AD. Funding is supported by The National Institute on Aging (U54 AG054345-01).

Speaker

Zackary Cope Research Scientist, University of Pittsburgh

Behavioral evaluation of a double-hit animal model of schizophrenia

Behavioral evaluation of a double-hit animal model of schizophreniaNatalia Cordero 1,2, J. Javier Meana 1,2,3, Carolina Muguruza 1,2, Jorge E. Ortega 1,2,3.1 Department of Pharmacology, University of the Basque Country UPV/EHU, Leioa, Bizkaia, Spain2 Centro de InvestigaciÃ³n BiomÃ©dica en Red de Salud Mental (CIBERSAM), Spain3 Biocruces Bizkaia Health Research Institute, SpainMaternal prenatal infections represent a risk factor that in combination with stressful events during adolescence may lead to the onset of schizophrenia in offspring. We aimed to characterize a novel double-hit animal model of schizophrenia in male and female mice, based in maternal immune activation (MIA/hit-1) with 7.5 mg/kg i.p. polyriboinosinic:polyribocytidilic acid [poly(I:C)] at gestational day 9.5, followed by social isolation (SI/hit-2) during 8 weeks in the peripubertal period. Four experimental groups (hit-1, hit-2, double-hit and control) were tested for social withdrawal'"Social Preference Test (SPT)'"and cognitive status'"Novel Object Recognition Test (NORT) and Y-Maze Spontaneous Alternation Test (YMSAT)'". Moreover, locomotor response to acute amphetamine (5 mg/kg i.p.) was also evaluated. The social exploration time in the SPT was decreased associated to hit-1 and hit-2, considered independently, in both male and female mice. Hit-1 and hit-2 significantly reduced the NORT discrimination index (DI) in an independent manner and regardless of the sex. Of note, both male and female double-hit models showed worse scores in SPT and NORT compared to single-hit groups. No differences were found in the spontaneous alternation in the YMSAT. Male mice showed increased basal locomotor activity associated to hit-1, while female mice had enhanced locomotor response to amphetamine associated to hit-2. These results showed an impact induced by MIA and SI on schizophrenia-related behaviors at adulthood in both sexes. These data support the double-hit model as a valuable translational tool in schizophrenia research.Natalia Cordero is recipient of a predoctoral fellowship of the Spanish Ministry of Science, Innovation and Universities (Grant PRE2018-084002) and Carolina Muguruza is recipient of an individual fellowship from the Marie Slodowska-Curie Programme (European Union's Horizon 2020, Grant 747487).

Speaker

Natalia Cordero PhD student in pharmacology, University of the Basque Country (UPV/EHU)

Prelimbic cortical projections to rostromedial tegmental nucleus play a suppressive role in cue-induced reinstatement of cocaine seeking

Prelimbic cortical projections to rostromedial tegmental nucleus play a suppressive role in cue-induced reinstatement of cocaine seeking.Adelis M. Cruz, 1, Haley F. Spencer, 1, Tabitha H. Kim, 1, Thomas C. Jhou, 3, Rachel J. Smith, 1,21 Department of Psychological and Brain Sciences, 2 Institute for Neuroscience, Texas A&M University, College Station, TX3 Department of Neurosciences, Medical University of South Carolina, Charleston, SCThe prelimbic cortex (PL) has been implicated in the regulation of drug-seeking behavior and has been shown to play roles in both promoting and suppressing drug-seeking. We hypothesized that these opposing roles may be supported by distinct efferent projections. Using classic retrograde tracers (cholera toxin B and Fluorogold), we found that within PL there are distinct neuronal subpopulations projecting to either the nucleus accumbens core (NAc core) or the rostromedial tegmental nucleus (RMTg). Previous studies have shown that PL projections to NAc core promote reinstatement of cocaine seeking in rats. In contrast, RMTg has been implicated in behavioral inhibition and has been shown to suppress reinstatement of cocaine seeking in rats. Therefore, we hypothesized that PL projections to RMTg may be involved in the suppression of drug seeking. In this study, we used a functional disconnection technique to temporarily disrupt the PL-RMTg pathway during cue- or cocaine-induced reinstatement. Male Sprague Dawley rats self-administered cocaine during daily 2-hour sessions, in which each lever press was reinforced by an intravenous infusion of cocaine (0.2 mg, fixed ratio 1) paired with tone/light cues. Following 12-15 days of self-administration, rats underwent extinction training for 7-14 days, during which no cocaine or cues were available. Reinstatement of extinguished cocaine seeking behavior was elicited by cues or cocaine prime (10 mg/kg, i.p.). To temporarily disrupt the PL-RMTg pathway during reinstatement, rats received a unilateral microinjection of GABA agonists in PL (baclofen 1 mM + muscimol 0.1 mM) and a contralateral microinjection of AMPA receptor antagonist in RMTg (NBQX 1 mM). We found that functional disconnection of the PL-RMTg pathway enhanced cue-induced reinstatement, as compared to vehicle injections, but had no effect on cocaine-induced reinstatement or extinction responding, indicating that the PL-RMTg pathway plays a suppressive role in cue-induced cocaine seeking specifically. Taken together with previous evidence demonstrating that PL projections to NAc core promote drug seeking, these data

indicate that PL supports opposing behavioral functions in cocaine seeking via distinct projections.Funding: National Institutes of Health DA037744 grant

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Speaker

Adelis Cruz PhD Student, Texas A&M University

Neurobiological correlates of pain avoidance behavior in alcohol- and opioid- withdrawal

Neurobiological correlates of pain avoidance behavior in alcohol- and opioid- withdrawalJA Cucinello-Ragland 1; ME Berner 1; AR Pahng 1; KN Edwards 1; S Edwards 1. 1 LSU Health Sciences Center-New Orleans, New Orleans, LA 70123 In contrast to their analgesic effects, chronic use and withdrawal of either opioids or alcohol creates the paradoxical emergence of a heightened state of pain sensitivity, termed hyperalgesia. Traditional methods of measuring pain behavior in animals ignores one of the hallmark symptoms of hyperalgesia, the development of motivational strategies to avoid pain. Using the mechanical conflict avoidance system (MCS), we quantify pain avoidance-like behavior as the latency for rats to exit an aversive brightly lit start chamber onto nociceptive probes, which they then must cross in order to enter a dark goal box. The present study seeks to identify differential effects of morphine and alcohol withdrawal on pain avoidance behavior and correlating neurobiological alterations. We found that adult male Wistar rats will display distinct patterns of pain avoidance-like behavior in morphine- and alcohol- withdrawal, where morphine-withdrawal produces a hyperalgesic behavior and ethanol-withdrawal produces an allodynic behavior. Because the amygdala controls motivational aspects of pain, we analyzed protein expression in both the central amygdala (CeA) and basolateral amygdala (BLA). In alcohol dependent animals, we found that pain avoidance-like behavior is positively correlated with BLA ERK phosphorylation and negatively correlated with the BLA ratio of endocannabinoid (eCB) synthetic:catabolic enzymes. However, these correlations were not observed in the BLA of morphine dependent animals or in the CeA of either morphine or alcohol dependent animals. Alternatively, we examined the periaqueductal grey (PAG), a region responsible for integrating ascending and descending nociceptive signals, and found that only pain avoidance-like behavior negatively correlated with PAG expression of eCB synthetic enzyme and cannabinoid receptor 1 only in morphine dependent animals. Overall, these findings suggest that morphine- and alcohol- withdrawal create differing patterns of pain avoidance-like behavior that may be due to differential neurobiological adaptations. This project was supported by T32AA007577, R00AA020839, R01AA025996, R21AA025736, NIH-NICHD-2018-05.

Speaker

Jessica Cucinello-Ragland LSUHSC-New Orleans

The effect of the 1st sexual experience on mating behavior and gene expression in male medaka fish (Oryzias latipes)

The effect of the 1st sexual experience on mating behavior and gene expression in male medaka fish (Oryzias latipes)Masahiro DAIMON 1, Satoshi ANSAI 1, Hirotaka SAKAMOTO 2, Takafumi KATSUMURA 3, Hideaki TAKEUCHI 1,2. 1 Tohoku University, 2 Okayama University, 3Kitasato University. Most animals grow from juvenile to adults with behavioral maturation, especially in sexual behaviors. It is well studied that sex hormones mainly make the secondary sex characteristics and mature the neural network underlying the reproductive behaviors. On the other hand, a little attention has been paid to the mechanism of how mating experience could influence neural/behavioral maturation. To approach this issue, we use medaka fish, a model animal for molecular genetics. Firstly, we examined whether naÃ¯ve (virgin) medaka males could improve their courtship behavior with their mate experience. We performed behavioral experiments using pairs of the naÃ¯ve male and sexually-mature female continuously 7 times (7 days) and the pairs of mating partners were fixed during the experiment. The latency to mate significantly decreased depending on the mating experience, while the degree of female receptivity was not changed. Furthermore, there was

a tendency to shortening latency to the 1st courtship, suggesting a male behavioral maturation. Therefore, we first demonstrate the medaka male can mature his behavior by the first mating experience itself. Secondly, to clarify the molecular basis underlying the behavioral maturation, we performed RNA-seq using the whole brains with the pituitary of naÃ¨ve and experienced male and identified 71 DEGs (differentially expressed gene). Among the DEGs, some genes associated with thyroid hormone system were up-regulated with mating experience. Interestingly, in various vertebrates, thyroid hormone system can activate maturation of reproductive organs and behaviors, which is triggered by especially photoirradiation with seasonal change. Here our findings firstly suggested that the mating experience itself triggers maturation of reproductive behavior via thyroid hormone system. Funding: This work was supported by the National Institute for Basic Biology Priority Collaborative Research Project 10-104 and Cooperative Research Project 19-347; Joint Research Grant 01111904 by the National Institutes of Natural Sciences; Japan Society for the Promotion of Science (JSPS) KAKENHI Grants 18H02479 (to H.T.), 16H01276 (to H.T.)

Speaker

Masahiro Daimon Ph.D student, Graduate School of Life Sciences, Tohoku University

Eukaryotic initiation factor 4E-binding proteins mediate behavioural changes in mice exposed to chronic variable stress

Eukaryotic initiation factor 4E-binding proteins mediate depressive behaviours in mice exposed to chronic variable stressAyeila Daneshmend 1, Emily Arsenault 1, Molly Zhang 1, Michael Parkhill 1, Edna Matta-Camacho 1, Stephanie Simard 1, Natalina Salmaso 1, Argel Aguilar-Valles 1. 1 Carleton University.Major depressive disorder (MDD) is one of the most common mental illnesses worldwide and chronic stress has been correlated with an elevated risk of developing depression. Ketamine, an N-methyl-D-aspartate receptor antagonist, has been demonstrated to rapidly reduce depressive symptoms in individuals with treatment-resistant MDD. Previously, we demonstrated that ketamine exerts antidepressant-like behavioural effects through regulation of negative regulators of protein synthesis termed eukaryotic initiation factor 4E binding proteins (4E-BPs) in naÃ¨ve mice. However, it is unclear whether this mechanism extends to depressogenic conditions, such as chronic variable stress (CVS). Therefore, we tested how male mice lacking 4E-BP1 and 4E-BP2 (Eif4ebp1/2 double knock out [DKO]) responded to CVS and ketamine. CVS consisted of 2 different stressors per day, for 5 weeks. Stressors included cage tilting, 15-minute restraint, wet bedding, no bedding, forced swimming, exposure to odour-induced variation, and altered light/dark cycle. Twenty-four hours after the last stressor, wildtype and Eif4ebp1/2 DKO mice received either a saline (IP, 10 ml/kg of body weight) or ketamine (IP, 10 mg/kg) injection, and were observed one hour later during a splash test. We found that in wildtype mice, CVS reduced grooming time in the splash test. In contrast, Eif4ebp1/2 DKO mice presented increased grooming in the splash test at baseline and this behaviour was not significantly changed by CVS or ketamine. Our results suggest that 4E-BPs are central in determining the response to ketamine and may be critical mediators of chronic stress.

Speaker

Ayeila Daneshmend Student , Carleton University

Rosmarinic Acid Improves hippocampal-Dependent Memory in D-Galactose Induced Aging Mice Model: An Effective Treatment Approach for Alzheimer Disease

Rosmarinic Acid Improves hippocampal-Dependent Memory in D-Galactose Induced Aging Mice Model: An Effective Treatment Approach for Alzheimer DiseaseShandhya Debnath, Dr. Md Ashrafur Rahman*, Sirajum Munira, Khadiza Akhter, Amzad HossainDept. of Pharmaceutical Sciences, North South UniversityThe rising percentage of the aging population is a global health concern because of developing the neurological disorder like Alzheimer's disease (AD). Evidence suggested that cholinergic dysfunction and abnormal oxidative stress biomarkers in the hippocampus were responsible for AD. Study showed that Rosmarinic

Acid (RA) improved the acetylcholine level and changed the oxidative biomarkers in brain. The objective of this study to investigate a safe and effective treatment approach for the management of age induced AD by using RA. We considered 4 different groups; Gr.1 (n = 8) were injected saline (0.2 mL/mouse), Gr.2 (n = 8) were injected D-galactose (100 mg/kg; subcutaneously) and saline (0.2 mL/mouse; intragastrically) simultaneously, Gr.3 (n = 24) were injected D-galactose (100 mg/kg) and simultaneously with three different doses of RA (intragastrically) defined as Gr.3a (n = 8): 100mg/kg RA; Gr.3b (n = 8): 200 mg/kg RA, and Gr.3c (n = 8): 400 mg/kg RA. Gr.4: (n = 8), were administered 150mg/kg/day piracetam (i.p). Memory level were examined by using Passive Avoidance (PA) and the Contextual Fear Conditioning (CFC) tasks. The biomarkers (SOD, MDA, and GSH) levels were assessed in the hippocampus. We plotted the dose response curve and found that Gr.3c showed higher response compared to 3a and 3b. In PA, Gr.3c showed a remarkable retention time (RT) compared to Gr.2 after 24 hrs (273.87Â±11.53 vs 119.75Â±4.92 sec; pË,0.001), 48 hours of training (257.19Â±9.28 vs 107Â±4.12 sec; pË,0.001) which were comparable to Gr.4 (p>0.05). Similarly in CFC: Gr.3c showed a significant freezing response compared to Gr.2 in Day 2 (78.47Â±5.00 vs 36.04Â±4.12 %; p<0.005), Day 31 (75.17Â±4.56 vs 35.41Â±4.29 %; p<0.005) which were comparable to Gr.4 (p>0.05). The biochemical data revealed that compared to the Gr.2, the MDA was decreased significantly (28.50Â±10.17 vs 125.18Â±6.75 nmol/ml; p<0.005), the SOD (27.03Â±3.35 vs 9.54Â±4.10 U/30 sec; p<0.005) and the GSH (11.92Â±0.70 vs 2.59Â±0.88 Âµmol/mg; p<0.005) were increased in Gr.3c and comparable to the Gr.4 (p>0.05) in the hippocampus. RA improves the memory in aging mice via modulating oxidative biomarkers in brain. Funded by NSU, NST

Speaker

Shandhya Debnath Graduate student, Research Assistant, North South University

Identifying a Role of Prefrontal Parvalbumin Neurons in Modulating Target Discrimination

Identifying a Role of Prefrontal Parvalbumin Neurons in Modulating Target Discrimination Tyler Dexter1, Daniel Palmer1, Amy Reichelt1, Lisa Saksida1, Tim Bussey1. 1University of Western Ontario. The prefrontal cortex (PFC) is a major modulator of attention, and the local synchronization of neuronal firing at gamma (30hz) frequencies is shown to correlate with engaging in attention-based tasks. It's been demonstrated that inhibitory neurons expressing the protein parvalbumin (PVIs) are heavily involved in generating synchronous firing in local neurons at the gamma frequency, indicating these neurons may facilitate PFC-dependent cognition. The project aimed to assess how prefrontal PVIs contribute to target detection and discrimination during an automated touchscreen attention task. Mice were assessed on the rodent continuous performance task (rCPT), where images are continuously presented on a touchscreen and mice are required to selectively respond to one image type (target) while suppressing responses to all others (non-targets). In vivo optogenetics was used in mice modified to express either inhibitory or excitatory opsins specifically on PVIs. Mice were implanted with bilateral fibers in the medial PFC and optogenetic stimulation of PVIs was either constant inactivation or frequency specific activation at the gamma (30hz) or theta (5hz) frequencies. Stimulation occurred immediately prior to and during the stimulus presentation period, and performance was compared between responses made with vs. without optogenetic stimulation, within a single session. Inactivation and 5hz activation of prefrontal PVIs significantly impaired target detection and discrimination in a simplified version of the rCPT (1 non-target), while 30hz activation had no effect. Interestingly, when task difficulty was increased by adding additional non-targets and lowering target probability (4 Non-targets, 33% target probability), 30hz stimulation significantly improved target detection and discrimination, while 5hz stimulation continued to impair target discrimination. These data indicate that prefrontal PVIs support visual attention in a frequency dependent manner. Under conditions of increased attentional load, a bidirectional effect on attention performance was observed between gamma and theta activation, indicating gamma frequency activity of prefrontal PVIs is necessary for optimal attention. This project was funded by the Ontario Graduate Scholarship and CIHR Project Grant.

Speaker

Tyler Dexter PhD Candidate, University of Western Ontario

Role of orexin in cognitive flexibility, sensorimotor gating, and impulsivity.

Role of orexin in cognitive flexibility, sensorimotor gating, and impulsivity. Archana Durairaja 1, Alexandrina Demidova 2, Markus Fendt 3. 1 Institute for Pharmacology and Toxicology, Otto-von-Guericke University, Magdeburg, Germany. 2 Institute for Pharmacology and Toxicology, Otto-von-Guericke University, Magdeburg, Germany. 3 Institute for Pharmacology and Toxicology, Otto-von-Guericke University, Magdeburg, Germany. Center of Behavioral Brain Science, Otto-von-Guericke University, Magdeburg, Germany. Deficits in cognitive flexibility, impaired sensorimotor gating and increased impulsivity are behavioral endophenotypes of several neuropsychiatric disorders including schizophrenia and attention-deficit/hyperactivity disorder (ADHD). Although, several transmitter systems in-cluding dopamine and noradrenaline are shown to be regulating these behavioural endopheno-types, there is not much known about the role of neuropeptides. The orexin neuropeptides, which are brain-widely released by neurons in the lateral hypothalamus, are major player in maintaining sleep/wake cycle, feeding behavior, arousal, and motivational behavior. Recent studies indicated that disruption of orexin signaling in basal forebrain impaired attention and cognition. In order to further investigate the role of orexin, we tested male and female orexin-deficient mice in established paradigms of cognitive flexibility (attentional set shifting task; ASST), sensorimotor gating (prepulse inhibition of the startle response; PPI) and atten-tion/impulsivity (5-choice serial reaction time task; 5-CSRTT). We found that orexin deficien-cy impaired the intra-dimensional shift phase (transfer of attention within the same perceptual dimensions) of the ASST in female but not in male orexin-deficient mice.'¯Of note, the indi-vidual mean performance in ASST neither correlated with trait anxiety nor with the narcolep-tic episodes in orexin-deficient mice.'¯Furthermore, when tested for PPI, orexin deficiency re-duced sensitivity to amphetamine-induced PPI deficit in males but not in females. However, orexin deficiency did not affect the amphetamine-induced higher locomotor activity in both sexes. Currently, we are also testing orexin-deficient mice in 5-CSRTT to investigate impul-sivity. So far, our results show that brain-wide orexin deficiency attenuates a specific form of cognitive flexibility and psychostimulant induced changes in sensorimotor gating in a sex-dependent manner. This work was funded by Deutsche Forschungs Gemeinschaft (FE 483/10-1 and SFB779).

Speaker

Archana Durairaja Institute for Pharmacology and Toxicology, otto-von-Guericke University

Sex-specific effects of early life adversity on hormones and reproductive function

Sex-specific effects of early life adversity on hormones and reproductive functionAuthors: Samantha Eck1, Jamie Palmer1, Cory Ardekani1, Sandra Luz2, Madeleine Salvatore1, Eric Kim1, Sydney Famularo1, Seema Bhatnagar2, Debra Bangasser11 Temple University Department of Psychology2 Children's Hospital of Philadelphia, Department of Anesthesiology and Critical Care MedicineEarly life adversity can alter development and has been linked to changes in hormonally-regulated endpoints including pubertal timing and reproductive behaviors. These effects depend on both the timing and type of adversity experienced, yet the mechanisms by which these changes occur is not well understood. To investigate this, we used the limited bedding and nesting (LBN) model, in which rat dams and pups are housed in a limited resource environment, without sufficient nesting material, from postnatal days 2 through 9. This manipulation is compared to rats raised in standard laboratory housing conditions with ample nesting materials. LBN does not seem to have a lasting impact on reproductive function in females, as the manipulation had no effect on either the timing of pubertal onset as measured by vaginal opening, or average estrous cycle duration in adulthood. LBN males, however, exhibit increased plasma estradiol levels in adulthood, suggesting that the LBN manipulation may have more of a lasting impact on male reproductive function. To further investigate this idea, we quantified the effect of LBN on male sexual behavior in adulthood and preliminary data show that LBN males exhibit a shorter latency to mount, intromit, and ejaculate than their control counterparts. This heightened sexual behavior may represent an evolutionarily adaptive response to a limited resource environment, with LBN males enhancing their reproductive strategies to increase their chances of passing on their genes earlier in life. Ongoing studies are investigating whether LBN may also result in an adaptive shift in female reproductive strategies by enhancing maternal care behaviors in LBN offspring. Together, these results show that the LBN model of early life adversity alters hormonally-regulated endpoints in males more than in females.Funding Acknowledgements:This work was supported by T32 DA007237 (SRE) and NSF CAREER grant IOS-1552416 (DAB).

Speaker

Samantha Eck Graduate Researcher, Temple University

Long term CB2 receptor inhibition in adolescent rats impairs autoshaping task in adulthood.

Long term CB2 receptor inhibition in adolescent rats impairs autoshaping task in adulthood. Ellner Yerushalmi, Danna 1, Muhammad, Shoaib, 1, Thorpe, Hayley 1, Frie, Jude 1, Khokhar, Jibran 1. 1 Department of Biomedical Science, University of Guelph, Guelph, ON. Introduction: Adolescence is a critical period of development that is particularly susceptible to modulation by external insults. Adolescent exposure to stressors such as drugs and stress have been shown to result in deficits in adulthood. The endocannabinoid system (ECS) is crucial in adolescent neurodevelopment and moderates many other systems. The cannabinoid receptor type 2 (CB2R) has not been studied thoroughly as it has only recently been discovered to exist in the brain. The studies that have been conducted suggest it may play a significant role in the reward circuitry. Our study chose to depress the CB2R activity in adolescence, using SR144528 (an inverse agonist of the CB2R), followed by assessment of reward-related behaviours in adulthood to determine its role in adolescent development. Methods: 29 Male Sprague-Dawley were injected with either 3.2 or 6.4 mg/kg of SR144528 (n=7-8/group) or vehicle (1:1:18 '" Cremaphor : EtOH : Saline solution). Subcutaneous injections were administered daily from PND 28-41. In adulthood, starting at PND65, rats underwent either a Pavlovian auto-shaping or instrumental reward conditioning paradigm. Lever pressing and food dispenser entries were measured, and a repeated measures ANOVA was used to analyze the data. Results: SR144528 treated rats had significantly lower acquisition of lever pressing in the auto-shaping task, seen by far less lever pressing behaviour over time. Statistical analysis revealed a main effect of treatment group F(2, 19) = 5.964, p = .010. There was no significant difference between drug and vehicle groups with regards to food dispenser entries in the auto-shaping task. The instrumental learning task revealed no significant difference between drug treated and vehicle group's acquisition or extinction. Discussion: These results suggest that inverse agonism of the CB2 receptor during adolescence differentially affects Pavlovian and instrumental reward learning in adulthood. Thus, our results suggest that CB2 receptor activity plays a critical role in adolescent development and has long-lasting implications for reward circuitry functioning in adulthood. Acknowledgements: Supported by NSERC.

Speaker

Danna Ellner Yerushalmi University of Guelph

Behavioral tests assessing neuropsychiatric phenotypes in adolescent mice reveal strain- and sex-specific effects

Behavioral tests assessing neuropsychiatric phenotypes in adolescent mice reveal strain- and sex-specific effects Ahmed Eltokhi1,2*, Barbara Kurpiers2, Claudia Pitzer2*1 Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of TÃ¼bingen, TÃ¼bingen, Germany2 Interdisciplinary Neurobehavioral Core, Heidelberg University, Heidelberg, GermanyIn humans, infancy and adolescence are associated with major changes in synaptic functions and ongoing maturation of neural networks, which underlie the major behavioral changes during these periods. Among adult cases with neuropsychiatric disorders including autism spectrum disorder, schizophrenia, attention deficit hyperactivity, and bipolar disorders, 50% have developed behavioral symptoms and received a diagnosis before 15 years of age. However, most of the behavioral studies in mice modeling neuropsychiatric phenotypes are performed in adult animals, missing valuable phenotypic information related to the effect of synaptic maturation during development. Here, we explored which behavioral experiments assessing neuropsychiatric phenotypes can be performed during a specific window of development in adolescent male and female C57BL/6N, DBA/2, and FVB/N mice that are typically used as background strains for generating genetically-modified mouse models. The three wild-type strains were evaluated across anxiety, social behaviors, and cognitive functions covering the main behavioral impairments that occur in neuropsychiatric disorders. During adolescence,

these three strains displayed significant differences under certain behavioral paradigms. In addition, C57BL/6N and FVB/N, but not DBA/2 mice revealed some sex-related differences. Our results provide new insights into discrete behaviors during development and emphasize the crucial importance of the genetic background, sex, and experimental settings in the age-dependent regulation of different behaviors.

Speaker

Ahmed Eltokhi Postdoc, Hertie Institute for Clinical Brain Research, University of Tübingen

Maternal separation altered social behaviours under group-housing environments in adult male C57BL/6 mice

Maternal separation altered social behaviours under group-housing environments in adult male C57BL/6 mice. Endo, Nozomi1; Makinodan, Manabu2; Somayama, Nami1; Komori, Takashi2; Kishimoto, Toshifumi 2; Nishi, Mayumi1. 1 Dept. of Anatomy and Cell Biology, Nara Medical University, Japan, 2 Dept. of Psychiatry, Nara Medical University, Japan. Adverse experience in early life can affect a formation of neuronal circuits during postnatal development and exert long-lasting influences on neural functions, which induces a variety of psychiatric disorders including depression, anxiety disorder, and PTSD. Many studies demonstrate that daily repeated maternal separation (MS), an animal model of early life stress, can alter in various emotional behaviors in adulthood. However, behavioral phenotypes of the MS mice under a long-term group-housing condition are largely unknown because conventional behavioral examinations for the model mice are designed to be used under simplified artificial conditions for a short observation period. In this study, we applied our newly developed assay system to investigate the effects of MS in C57BL/6J male mice during infancy on later adult behaviors under group-housing conditions during four-day continuous observations. We found that the MS mice showed abnormalities in social proximity to other cagemates on Day 3 and Day 4 compared with the control mice. This phenotype of the MS mice does not appear during mice were strangers each other immediately after the start of the experiment, but seems to gradually appear when the social relationship between these mice changes day by day. This result indicates a phenotype that can be identified only by performing long-term behavioral analysis under group-housing. MS mice also exhibited alteration of approach preference in the novel environment, and lower social rank on Day1. The present findings demonstrate that analyses of animal models under a more ethologically relevant condition, such as a long-term group-housing with social context, should be considered when attempting to understand complex behavioural phenotypes in animal models. Future elucidation of the neural basis of these social behavioral abnormalities that appear in ordinary life will be important insights to understand the pathogenesis of psychiatric disorders. Funding: JSPS KAKENHI (17H07032, 19K16899 to N.E., 16H06403, 19H05226, 20H03604 to M.M., 20K16674 to T.K. and 17H06060, 17K19922, 19H03539 to M.N)

Speaker

Nozomi Endo Nara Medical University

Socializing reduces distress-associated behavior in mice

Socializing reduces distress-associated behavior in mice.Shokat Fadaei, Saba ; Wei, Haohan ; Adewakun, Ayo ; Froemke, Robert NYU Langone Medical Center Diseases are associated with significant changes in behavior. In animal models, such sickness behavior includes lethargy, arched or curled body posture, inactivity, and reduced amount of time that the animal consumes food or drinking water (Hart, 1988). Socializing has been associated with physical health and mental health benefits, improved learning, and reduced mortality (Karen A. Ertel, 2009) (Lisa F. Berkman, February 1979) (Dent, 2019). Yet, how socializing affects sickness behavior remains generally misunderstood. We studied how socializing modulates sickness behavior in an LPS-induced endotoxemia model known to produce an acute inflammatory response and cognitive impairment associated with neuroinflammation (Shannon Copeland, 2005) (Jiayi Zhao, 2019). A

total of 12 mice C57/BL6 mice (P60, obtained from Taconic (USA)) were divided into two groups: socially isolated mice or co-housed mice. Both groups were sub-divided and received either LPS injection or Saline injection. The intraperitoneal LPS sub-lethal dose for this study was 150 Âµl. Continuous seventy-two hours recording sessions were performed and videos were analyzed and scored by three people. We found that co-housing mice reduced the mortality ratio and decreased the duration of exhibition of the sickness behavior. Analysis showed that the single-housed mice displays sickness behavior for about thirty-five minutes following the LPS injection, while the co-house mice only spent twelve minutes displaying sickness behavior. In addition to that results the mice that were not co-housed were showing the hunched-posture for a longer period of time during the whole recording. We are currently investigating how co-housing mice will affect the recovery process.Moreover, motion tracking revealed that socially isolated LPS injected mice remained up to three to four hours in one spot in the home cage displaying sickness behavior. On the other hand, co-housed LPS injected mice exhibited such sickness behavior only for one hour.In conclusion, Co-housing the mice during the time of experiments will enhance the process of recovery from an endotoxemia.

Speaker

Saba Fadaei Research associate , NYU Langone Medical Center

Role of orexin in behavioral endophenotypes of neuropsychiatric disorders

Role of orexin in behavioral endophenotypes of neuropsychiatric disorders.Nadine Faesel 1,2, Malgorzata H. Kolodziejczyk 1, Michael Koch 2, Markus Fendt 1,31 Institute for Pharmacology and Toxicology, Otto-von-Guericke-University Magdeburg, Germany. 2 Department of Neuropharmacology, Brain Research Institute, University of Bremen, Germany. 3 Center for Behavioral Brain Sciences, Otto-von-Guericke-University Magdeburg, Germany.The orexin neuropeptide system is known for its crucial role in regulating the sleep/wake cycle and feeding behavior, but it is also important for a variety of other processes. Here, we focus on the potential involvement of orexin in behavioral endophenotypes of neuropsychiatric disorders, including panic-like anxiety and social (fear) behavior. For that, the effects of orexin deficiency in mice were tested in three different behavioral experiments: (1) anxiety behavior in the elevated plus maze (EPM) after intracerebroventricular injections of the panicogenic substance cholecystokinin-4 (CCK-4), (2) sociability and social novelty in a modified version of Crawley's sociability test, and (3) social fear conditioning in a novel paradigm. Experiment (1): In wild-type mice, CCK-4 injections increased anxiety-like behavior in the EPM and plasma corticosterone levels. These effects of CCK-4 were absent in female orexin-deficient mice, whereas male orexin-deficient mice still responded to CCK-4 treatment. Currently, we analyze CCK-4 induced c-Fos immunoreactivity with the aim to elucidate the neural pathways involved in panic-like anxiety. Taken together, our data indicate an important and sex-dependent role of orexin in panic-like anxiety, thus emphasizing orexin and its receptors as potential targets for future pharmacological therapies of human panic disorders. Experiment (2+3): Female orexin-deficient mice displayed reduced sociability and decreased preference for social novelty compared to their wild-type littermates, while those effects of orexin deficiency were absent in males. Secondly, orexin deficiency facilitated the acquisition and/or expression of conditioned social fear, while impairing its extinction in both sexes. In conclusion, our results indicate an important regulatory role of the orexin system in social (fear) behavior, which is further underlying the hypothesis of orexin being an integrator of motivation, affect, and emotion.This work is supported by the DFG (SFB 779, FE 483/7-1 & /10-1).

Speaker

Nadine Faesel PhD Student, Otto-von-Guericke-University Magdeburg & University of Bremen

Chemogenetic manipulation of pre-limbic cortex increases impulsive choices following time-based intervention training in rats

Chemogenetic manipulation of pre-limbic cortex increases impulsive choices following time-based intervention training in rats. Laura Favreau, Cathryn Haas, Kelsey Panfil, Travis Smith, Aubrey Deavours, Kimberly Kirkpatrick. Kansas State University. Time-based interventions have been developed to moderate impulsive choices with promising results, but little or no research has examined the neural substrates that may underlie the intervention effects. The prelimbic (PL) region of the prefrontal cortex is a good candidate due to its role in time discrimination coupled with top-down connections with the nucleus accumbens core, which is heavily implicated in impulsive choices. We infused an inhibitory DREADD (Designer Receptors Exclusively Activated by a Designer Drug) virus (AAV-CaMKIIa-hM4D(Gi)-mCherry) and a sham control virus (rAAV-CaMKIIa-EGFP) into PL in rodents that had previously received a time-based intervention. The DREADD was activated with Clozapine-N-Oxide (1 mg/kg) prior to impulsive choice testing in which rats chose between a larger-later (LL) reward of two pellets after 30 s and a smaller-sooner (SS) reward of one pellet after an increasing delay (10, 15, 20, 25, and 30 s). Following the choice task, rats were euthanized, brains were perfused, and placement of the viruses was assessed with fluorescent microscopy. The DREADDs group made fewer LL choices and showed reduced delay sensitivity compared to the sham group, suggesting that the CNO inhibition of PL may have blocked the intervention effects on choice. Although further controls are needed before definitive conclusions can be drawn, this study suggests that the PL is a promising candidate for regulation of the time-based intervention effects on impulsive choices. This project was supported by NIH grants MH085739 and GM113109.

Speaker

Laura Favreau Kansas State University

Anxiolytic-like effects of the positive GABA-B modulator GS39783 are dependent on individual baseline anxiety levels

Anxiolytic-like effects of the positive GABA-B modulator GS39783 are dependent on individual baseline anxiety levels. Markus Fendt 1,2, Ahmet Oğuzhan Bıçakcı 3, Yu-Hsin Chang 3, Evelyn Kahl 1, Mousumi Sarkar 3. 1 Institute for Pharmacology and Toxicology, 2 Center for Behavioral Brain Sciences,3 Integrative Neuroscience Program, Otto-von-Guericke University Magdeburg, Germany.

Fear and anxiety are emotions that help animals and humans to cope with threatening situations. However, excessive fear and anxiety are symptoms of several neuropsychiatric disorders including anxiety and stress-related disorders. A putative target for new drug development is the GABA-B receptor that has allosteric binding sites. During the last decade, positive GABA-B receptor modulators were tested in a number of different laboratory paradigms for fear and anxiety; however, the reported effects were not consistent.The aim of our study was to understand the variability in the reported effects. For this, we treated female and male C57Bl/6 mice with the positive GABA-B modulator GS39783 and submitted them to a variety of behavioral paradigms used in fear and anxiety research: (I) elevated plus maze, (II) light-dark box, (III) predator odor induced avoidance, (IV) sociability, and (V) contextual fear and safety conditioning. At a group level, we did not find anxiolytic-like effects in any of the paradigms. However, we observed that the vehicle-treated control animals only expressed weak levels of anxiety. For further analysis, we therefore grouped the animals based on their individual anxiety levels under control conditions in groups with high, medium and low anxiety. GS39783 treatment had only significant anxiolytic-like effects in the high anxiety group. In a further experiment, we first exposed the mice to aversive electric stimuli. Ten days later, the GS39783 effects in the light-dark box were tested. The anxiolytic-like effects of GS39783 were highly correlated with the pre-exposure effects on light-dark box behavior. That is, GS39783 had anxiolytic-like effects in stress-responsive animals but not in stress-resistant animals. Taken together, these data show that GS39783 effects are dependent on baseline anxiety levels. Whereas low or medium (normal) levels of anxiety were not affected by GS39783, high levels of anxiety were efficiently reduced by GS39783 treatment.This project was supported by Helse Nord, Norway (HNF1426-18).

Speaker

Markus Fendt Group Leader & adj. Professor, University of Magdeburg

The Effects of Time-Based Interventions on Self-Control and Choice Latency in an Impulsive Choice Task

The effects of time-based interventions on self-control and choice latency in an impulsive choice task. AndersonFitch 1,2, KourtneyRumback 1,2, TravisSmith 1,2, KimberlyKirkpatrick 1,2. 1 Kansas State University, 2 Kansas State University, 3 Kansas State University, 4 Kansas State University. In preclinical research using rats, time-based interventions that deliver experiences with delayed rewards often promote self-control [i.e., a preference for a larger-later (LL) reward over a smaller-sooner (SS) reward] in impulsive choice tasks. It is hypothesized that the interventions improve cognitive control over decision-making. A recent study featuring a time-based intervention and choice task utilizing a 5-s SS delay unexpectedly increased impulsive choices in contrast with a similar study featuring a 10-s SS delay that increased self-controlled choices. The present study examined time-based intervention effects on impulsive choices in groups assigned to either a 5-s SS delay (implicated in increasing impulsive choices) or 10-s SS delay (implicated in decreasing impulsive choices). The rats in the 10-s SS delay intervention group increased self-control (more LL choices) compared to both pre-intervention baseline choices and to the 5-s SS delay group. Furthermore, the improvement in self-control corresponded with lengthening of choice latencies. This suggests that time-based interventions may promote self-control in part through strengthened functionality in frontal areas involved in inhibitory control. In other words, rats learned to inhibit the impulsive preference for the SS when the SS was 10 s. Choice latency data are easily derived from most impulsive choice data sets and analyses of such data provide an avenue to evaluate and explore mechanisms contributing to impulsive choice. Future latency analyses should assess the replicability of these findings within time-based interventions and the generalizability of these findings to qualitatively different interventions effecting choice behavior. This project was supported by NIH grants MH085739 and GM113109.

Speaker

Anderson Fitch Kansas State University

Chronic oral administration of a novel estrogen receptor beta agonist enhances memory consolidation and alleviates vasomotor symptoms in a mouse model of menopause

Chronic oral administration of a novel estrogen receptor beta agonist enhances memory consolidation and alleviates vasomotor symptoms in a mouse model of menopauseAaron W. Fleischer1, Jayson C. Schalk1, Edward A. Wetzel2, Alicia M. Hanson3, Daniel S. Sem3, William A. Donaldson2, Karyn M. Frick11Department of Psychology, University of Wisconsin-Milwaukee, Milwaukee, WI, 532112Department of Chemistry, Marquette University, Milwaukee, WI, 532333Department Pharmaceutical Sciences, Center for Structure-Based Drug Design and Development, Concordia University Wisconsin, Mequon, WI, 53097Menopause is associated with hot flashes, cognitive decline, anxiety, and depression. Estrogen-based therapies reduce these symptoms, but also increase risks of cancer and other health issues due to the activation of the alpha (ERa), but not beta (ERb), estrogen receptor isoform. Thus, ERb-selective therapies are promising options to mitigate negative menopausal symptoms without the complications associated with ERb activation. Our goal here was to determine whether chronic treatment with EGX358, a novel highly selective ERb agonist, could reduce negative symptoms in a mouse model of menopause. 9-week-old ovariectomized C57BL/6 mice were gavaged daily for 10 weeks with vehicle, the highly potent estrogen 17b-estradiol (E2), the ERb agonist diarylpropionitrile (DPN), or EGX358. Hot flash-like symptoms were measured by thermal imaging of tail skin temperature (TSkin) after injection of vehicle or senktide, which induces hot flash-like symptoms. Anxiety-like behavior was assessed in the open field (OF) and elevated plus maze (EPM), and depression-like behavior was assessed in the tail suspension (TST) and forced swim tests (FST). Mice were also trained in object recognition (OR) and object placement (OP) tasks and tested for object and spatial memory, respectively. Compared to vehicle, E2, DPN, and EGX358 reduced senktide-mediated increases in TSkin and enhanced OP and OR memory. Although E2 increased time in the center of the OF, no other treatment affected behavior in the OF, EPM, TST, or FST compared to vehicle. Thus, chronic EGX358 treatment reduces hot flash-like symptoms and improves spatial and object recognition memories in ovariectomized mice. As such, ERb activation may be a promising avenue for reducing menopause-related hot flashes and memory

dysfunction.Supported by: NIH Grants 2R15GM118304-02 and R01MH107886, and a UWM Research Foundation/Bradley Catalyst Grant to KMF.

Speaker

Aaron Fleischer Graduate Student Researcher, University of Wisconsin-Milwaukee

Intermittent access to the opioid fentanyl induces a robust addiction-like state maintained by orexin/hypocretin receptor signaling

Intermittent access to the opioid fentanyl induces a robust addiction-like state maintained by orexin/hypocretin receptor signaling. Fragale, Jennifer; James, Morgan; O'Connor Shayna; Aston-Jones, Gary. 1,2,3,4 Brain Health Institute Rutgers University, 2 Florey Institute of Neuroscience and Mental Health. The intermittent access (IntA) self-administration paradigm was established to better model abuse patterns in human addicts and has since emerged as a robust preclinical model of drug addiction. We have shown that IntA to cocaine produces a robust addiction-like state dependent upon orexin (hypocretin) receptor signaling. Here, we sought to extend our behavioral characterization of the IntA model to the widely abused opioid fentanyl and to determine the role of the orexin system in the resulting IntA-induced addiction-like state. Male rats were either given IntA to fentanyl (5min of access separated by 25min of no-access) or continuous fentanyl access in 1h (short access; ShA), or 6h (long access, LgA) sessions for 14 days. IntA to fentanyl produced a greater escalation of fentanyl intake, increased motivation for fentanyl on a behavioral economics task, persistent drug seeking during abstinence, and stronger cue-induced reinstatement compared to ShA or LgA rats. Addiction-like behaviors induced by IntA to fentanyl were reversed by the selective orexin-1 receptor (OxR1) antagonist SB-334867, as well as the FDA-approved dual OxR1/OxR2 antagonist. Together, the data indicate that the IntA model is a useful tool in the study of opioid addiction and that the orexin system is critical for the maintenance of addiction behaviors induced by IntA to fentanyl. Moreover, these results provide support for the use of Ox1R antagonists in clinical populations, particularly among individuals with severe opioid addiction. Funding: NIH postdoctoral fellowship (K12 GM093854), National Institute on Drug Abuse (NIDA; K99DA045765) Fellowship, and by a U.S. Public Health Service Award from NIDA (R01 DA006214).

Speaker

Jennifer Fragale Postdoctoral Fellow, Rutgers University

Acute behavioural effects of cocaine in mice that lack vesicular zinc

Acute behavioral effects of cocaine in mice that lack vesicular zinc. Fu, Selena, 1, Thackray, Sarah E., 1, Dyck, Richard H., 1. 1 University of Calgary. Zinc is a ubiquitous trace element that serves vital and extensive structural and functional roles in all cells. In the brain, zinc has neuromodulatory effects and can act as a neurotransmitter. This is because zinc ions are sequestered into synaptic vesicles of a subset of glutamatergic neurons by zinc transporter 3 (ZnT3). Once packaged, vesicular zinc can be co-released with glutamate in an activity-dependent manner and has been implicated in the involvement of experience-dependent synaptic plasticity. Brain regions that contain high levels of vesicular zinc include the olfactory bulb, hippocampus, neocortex, amygdala, and striatum. To date, vesicular zinc research has mainly been directed to its role in the hippocampus and neocortex, while the role of vesicular zinc in the striatum has been less extensively studied. Thus, as a first step to understanding the role of vesicular zinc innervation in striatal function, we sought to examine the behavioral effects of cocaine in knockout (KO) mice, that lack vesicular zinc due to genetic deletion of ZnT3, compared to wildtype (WT) mice. Total locomotor activity in the open field test was assessed across 7 days in male and female ZnT3 KO and WT mice that received daily intraperitoneal injections of cocaine (20 mg/kg) or equivalent volumes of saline. Our results indicate that both male and female ZnT3 KO mice generally exhibited a reduced locomotor response to cocaine compared to WT mice. Male KO mice travelled significantly less distance on days 1 and 2 compared to male

WT mice, whereas female KO mice travelled significantly less distance on days 3 and 4 compared to female WT mice. Interestingly, male WT mice showed diminished response to cocaine across repeated administrations, whereas male ZnT3 KO mice showed a gradual increase in response suggesting differential tolerance and sensitization effects, respectively. We also found sex differences in how long cocaine acts acutely with female mice returning to baseline levels of locomotion much faster than male mice. These results demonstrate that vesicular zinc is involved in modulating the effects of cocaine, whereby cocaine differentially affects the locomotor responses of ZnT3 KO and WT mice. Furthermore, these effects are sex-dependent with a difference in the effects of cocaine in male and female ZnT3 mice.

Speaker

Selena Fu

Does Own Species Matter? Holistic Face Processing for Great Apes

Does Our Own Species Matter? Holistic Face Processing for Great Apes Evrim Gülbetekin, Enes Altun, M.Nurullah ErAkdeniz University Department of Psychology Social Neuroscience LaboratoryHumans have tendency to perceive faces holistically. This effect is called holistic processing and it has been widely demonstrated by the literature. On the other hand, this effect has not been studied for great ape faces with in the part-whole test. In this study, we examined whether human participants perceived all great ape faces (human, gorilla, chimpanzee, bonobo, and orangutan) holistically or not. In the part-whole test, a facial part was presented either in isolation or within the whole face. If the facial part is better recognized in the whole face condition then the part condition then that part is considered as being recognized holistically. Seventy five undergraduate students participated. Twenty faces of five species (human, gorilla, chimpanzee, bonobo, and orangutan) were presented in part and whole conditions and the participants' face recognition performance was measured for each species. There were 120 trials in total. Accuracy in part and whole trials were analyzed. The results of pairwise t-test for human faces indicated that the accuracy for the whole condition (M=.83, SD=.13) was significantly higher than the part condition t(74) = -4.385, p=.000, % 95 confidence interval (CI) = [-0,119, -0,044], Cohen's d = -0,506 showing that human faces were perceived holistically. But the same effect was not observed for the faces of the other species. We conducted pairwise t-tests to compare whole and part accuracy for each of the face parts in all species. We found that eyes were significantly better recognized in the whole condition (p=.001, p=.009, p=.042, p=.003 for human, bonobo, chimpanzee orangutan respectively) than the part condition except for gorilla faces. These results have shown that holistic face processing is specific to our own species however, the top part of the face including eyes seems to be critical in holistic processing for most of the great ape faces.

Speaker

Evrim Gülbetekin Associate Professor, Akdeniz University

Cognitive impairment and resting state EEG in people living with HIV

Cognitive impairment and resting state EEG in people living with HIV García-Gomar, M.L1; Negrete-Cortés, A.J1; Chávez-Méndez, J.R1; Cruz-Zúñiga, N1; González-García, D.A2; Berra-Ruíz, E1. 1 Facultad de Ciencias de la Salud, UABC 2 Facultad de Medicina y Psicología, UABC. Approximately 40-50% of HIV+ people present neurocognitive impairment (NCI). The cognitive domains most commonly impacted are learning, executive functions and working memory. Hispanics/Latinos living in the US are at higher risk for HIV-associated NCI. Rates of 33 to 66% of NCI have been reported in Mexico. Tijuana is considered as one of the Mexican regions with higher HIV incidence rates. The aim of the present study was to investigate rates, pattern of NCI and resting state EEG rhythms in Mexican HIV+ persons living in Tijuana. Participants were recruited from the board-and-care home 'œLas Memorias' house care. A total of 30 HIV+ men and women from a vulnerable Tijuana population participate in the study. After providing informed consent, each participant underwent a brief interview, a neuropsychological assessment and a 19 lead resting state EEG. Changes in

absolute power (PA), relative power (PR) and average frequency (FM) were studied. NCI was evident in 3.3% of HIV+ patients. The most affected cognitive domain was executive function (EF) with 64.3% of impairment. Regarding EEG analyses excess of delta and theta Absolute Power was found. In addition a significant positive relationship was found between the FE score and delta relative power. We found a less severe NCI than the one reported in the literature with the Latino population. This low percentage of NCI can be explained under the paradox of health reported in the Hispanic population. In the board and care home HIV+ patients live under one roof and share characteristics of the disease and social conditions which contribute to the formation of strong social support networks that could be protective for patients with HIV. The findings of the present study suggest a greater cognitive impairment in EF that are especially vulnerable to the structural and functional pathological changes that occur as a result of HIV infection. Finally, it is important to highlight the relationship between the functionality of daily life and the cognitive function for the future development of cognitive habilitation programs for HIV+ people. This research was supported by grants UABC 350/2/N/63/20, CNEIP_C2018_P004.

Speaker

Maria Luisa García-Gomar Full Time Professor, Universidad Autonoma de Baja California

Daily running vs. a potential exercise-memetic - testing the effectiveness of exercise and metformin at reversing obesity-induced impairments in neurogenesis and memory

Daily running vs. an exercise-memetic - testing the effectiveness of exercise and metformin at reversing obesity-induced impairments in neurogenesis and memory Olivia R Ghosh-Swaby1,2, Amy Reichelt1,2,3, Timothy J Bussey1,2,4, Lisa M Saksida1,2,41.Schulich School of Medicine and Dentistry, Western University, London, ON, Canada2.Robarts Research Institute & Brain and Mind Institute, Western University, London, ON, Canada3.Florey Inst Neuroscience and Mental Health, Melbourne, Australia4.BrainsCAN, Western University, London, ON, CanadaExcessive consumption of high fat and high sugar (HFHS) foods can cause weight gain and obesity, reduce adult hippocampal neurogenesis, and impair learning and memory. Here we examined whether two interventions known to boost hippocampal neurogenesis, aerobic exercise or the diabetes drug metformin, are capable of reversing HFHS diet-induced cognitive impairment in mice. To study the impact of exercise, mice were fed either a HFHS diet or control diet for 28 days and randomly assigned to either running wheel access for 3 hours, 5 days a week or no access. To study the effects of metformin, mice were fed either a HFHS diet or control diet and administered metformin (200mg/kg, i.p.) or saline for 28 days. Memory was then tested on a spontaneous location recognition (SLR) task, shown to be sensitive both to the consumption of a high sugar diet and changes in hippocampal neurogenesis. During a sample phase, mice explored an arena containing identical landmarks in 3 locations arranged in a triangular formation. After 3 hours, memory was tested by assessing the extent that mice can discriminate and remember the locations presented during sample. Cognitive load was varied across 3 conditions under which the similarity of the to-be-remembered locations was manipulated parametrically: dissimilar (ds-SLR), similar (s-SLR), or extra similar (xs-SLR). Following SLR, brain sections were immunohistologically examined using doublecortin as a marker of neuroproliferation (DCX+ cells). HFHS diet led to impairments in memory under s-SLR & xs-SLR conditions. In contrast, control-fed mice spent more time exploring the novel location during ds-SLR and s-SLR conditions. Mice that exercised exhibited enhanced memory and novelty exploration during xs-SLR. Both exercise and metformin reversed cognitive decline in HFHS-fed mice tested on ds-SLR and s-SLR. Interestingly, both exercise and metformin enhanced performance in xs-SLR in female mice fed a HFHS diet. However, the relationship between exercise- and metformin-induced increases in neurogenesis, and cognitive improvement, was not straightforward. Physiologically, exercise and metformin reduced HFHS diet-induced weight gain and adiposity. Our results indicate that exercise and metformin can reverse diet-induced cognitive impairment in a hippocampal-dependent task, but the neural mechanism by which metformin improved memory may not be associated directly with increased neuroproliferation.Funding: NSERC, BrainsCAN

Speaker

Olivia Ghosh-Swaby Western University

Functional Remodeling of the Tripartite Synapse in Cocaine Abuse and Addiction

Functional remodeling of the tripartite synapse in cocaine abuse and addictionGiangrasso, Danielle 1; Wilcox, Karen 1; Keefe, Kristen 11. University of UtahCocaine is a commonly abused psychostimulant, but current therapies for cocaine addiction are limited. With repeated drug exposure, there is a shift from drug abuse to addiction that is thought to develop via the transition from goal-directed to habitual control over behavior, respectively. It is widely recognized that addictive behaviors are under habitual control, and that this form of behavioral control is mediated by the dorsolateral striatum (DLS). The transition to habitual control over behavior is associated with potentiated cortico-striatal glutamate signaling in the DLS. However, the neural mechanisms underlying these changes in glutamate signaling during the development of addiction are largely unknown. The astrocytic glutamate transporter 1 (GLT-1) removes glutamate from the extracellular space, and, as such, regulates both the concentration and timecourse of extracellular glutamate. Rats with a history of cocaine self-administration display decreased GLT-1 expression and uptake capacity in the ventral striatum, an area involved in encoding the rewarding properties of drugs. Similarly, GLT-1 expression is decreased in DLS following cocaine self-administration, but it is unknown whether that cocaine self-administration was goal-directed or habitual. Therefore, the objective of this project is to investigate the role of GLT-1 in DLS of rats exhibiting goal-directed vs. habitual behavior control over cocaine-seeking behavior. Rats were trained to self-administer cocaine in a chained cocaine-seeking and taking paradigm, which yielded both goal-directed (~73%) and habitual (~27%) cocaine-seeking rats. Current experiments are underway to assess the expression of GLT-1 in the DLS of goal-directed and habitual cocaine-seeking rats and to investigate the clearance activity of GLT-1 in the DLS of goal-directed and habitual cocaine-seeking rats through iGluSnFr imaging. We hypothesize that rats with habitual control over cocaine-seeking behavior will have lower GLT-1 expression and lower GLT-1-mediated glutamate uptake in the DLS than rats with goal-directed control over cocaine-seeking behavior and yoked saline controls.We would like to acknowledge our funding from the National Institutes of Health, R21DA046600

Speaker

Danielle Giangrasso PhD candidate, University of Utah Neuroscience Program, University of Utah

Effects of methamphetamine-induced dopamine toxicity on striatal plasticity.

Effects of methamphetamine-induced dopamine toxicity on striatal plasticity. Anne S. Gibson 1,2, Peter J. West 1,2,3, and Kristen A. Keefe 1,2 1 Interdepartmental Program in Neuroscience, University of Utah 2 Department of Pharmacology and Toxicology, University of Utah 3 Anticonvulsant Drug Development Program, University of Utah Methamphetamine (METH) is a highly addictive psychostimulant. Cognitive deficits are apparent in individuals with a history of METH abuse, and targeting cognitive function may be an efficacious approach to managing METH abuse and addiction. However, in order to develop a successful treatment for METH abuse, the consequences of METH-induced neurotoxicity must be better understood. METH exposure is known to be associated with damage to central monoamine systems, particularly dopamine signaling. Rodent models of such damage have revealed a decrease in the amplitude of phasic dopamine signals and significant striatal dysfunction, including changes in molecular, systems, and behavioral functions of the striatum. Phasic dopamine signals activate dopamine D1 receptors, which are involved in striatal synaptic plasticity, particularly long-term potentiation (LTP) in D1 receptor-expressing striatal medium spiny neurons. We hypothesize that METH-induced dopamine neurotoxicity will diminish D1 receptor-dependent striatal plasticity in mice. To test this, mice were treated with a METH binge regimen (4 x 10 mg/kg d,l-methamphetamine, s.c.). This binge regimen provides a reliable rodent model that recapitulates all of the known METH-induced neurotoxic effects observed in humans, including dopamine toxicity. Three weeks later, plasticity was assessed using white matter high frequency stimulation (HFS) and striatal field recordings. Under these conditions, LTP was induced in the dorsomedial striatum of saline-pretreated, but not METH-pretreated mice. Further, the LTP observed in saline-pretreated mice was abolished by the dopamine D1 receptor antagonist SCH23390, indicating that this LTP is D1 receptor-dependent. Finally, preliminary data suggest that acute, in vivo treatment with bupropion (50mg/kg i.p.) can restore LTP in striatal slices from METH-pretreated mice. Together these studies suggest that METH-induced neurotoxicity impairs D1-dependent LTP within the dorsomedial striatum, and that LTP can be

restored with the FDA-approved drug bupropion.Funding: American Foundation for Pharmaceutical Education; University of Utah Health Sciences

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Speaker

Anne Gibson Graduate Student, University of Utah

New methods to study the organization of behavior in laboratory rats: An ethological approach

New methods to study the organization of behavior in laboratory rats: An ethological approach. Melissa J. Glenn 1, Dave G. Mumby 2, Amanda L. Doak 1. 1 Department of Psychology, Colby College, Waterville, Maine USA, 2 Department of Psychology, Concordia University, Montreal, Quebec Canada. In the fields of psychology, biology, and neuroscience, there are persistent concerns about the extent to which research findings using animal models can aid our understanding and treatment of human conditions. The alarming accumulation of failed clinical trials in humans after success in animal models has even been identified by some as a 'œtranslational crisis'. These failures likely have many contributing factors; a major factor may be the drift in behavioral neuroscience research toward reducing complex behavioral processes to very basic metrics. Our technological prowess in biology and neuroscience and extraordinary progress in understanding cellular and molecular processes are far outpacing behavioral research and to best leverage gains made in understanding complex biological problems requires more sophistication in our animal models. I will describe our efforts to address this problem by 1) adopting housing conditions for laboratory rats that promote natural behaviors, such as burrowing, trail making, nesting, and social diversity; and 2) moving beyond husbandry by studying rats in these semi-natural habitats to better understand and assess how they organize their behavior. This research was supported by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under grant number P20GM103423 and by a James McKeen Cattell sabbatical award to MJG.

Speaker

Melissa Glenn Associate Professor of Psychology, Colby College

Effect of escapable and inescapable stress on perineuronal nets and parvalbumin in the rat medial prefrontal cortex

Effect of escapable and inescapable stress on perineuronal nets and parvalbumin in the rat medial prefrontal cortex.Abigail H. Gligor1, Michael V. Baratta2, Ashlynn Dean1, and Barbara A. Sorg11Legacy Research Institute, Portland, OR 97232; 2Department of Psychology and Neuroscience, University of Colorado, Boulder, CO 80301Exposure to inescapable stress (IS) produces anxiety- and depressive-like behavior in male rats, whereas escapable stress (ES) attenuates such behaviors even after subsequent IS. ES increases activity in the medial prefrontal cortex (mPFC), which confers resilience to future stressors via top-down inhibition over dorsal raphe nucleus activity. Parvalbumin (PV) neurons powerfully regulate output of the mPFC and may therefore contribute to the impact of ES in stress resilience. Here we determined the extent to which IS and ES altered PV levels and their surrounding perineuronal nets (PNNs), extracellular matrix structures that stabilize PV synaptic connections and heavily regulate excitatory:inhibitory balance. We used three groups of rats: a home cage control group; an ES group (100 tails shocks that could be terminated by the rat rotating a wheel); and a yoked IS group (the same shocks given to ES-treated rats but with a wheel that had no consequences when rotated). Cells in the mPFC were triple-labeled for c-Fos, PV, and PNNs (the latter with Wisteria floribunda agglutinin). IS rats had increased c-Fos intensity, but decreased PV and PNN intensity compared to control and/or ES rats. The increased c-Fos intensity suggests a higher activation in mPFC PV interneurons, and lower PNN intensity may enhance plasticity of PV interneurons in IS rats. No difference in cell numbers were observed between groups. Further understanding of the mechanism and neuronal phenotypes underlying stress resiliency is expected

to allow us to identify new therapeutic targets for stress-related disorders.Grant support: NIH DA040965 (BAS); NIH MH050479 (MVB)

Speaker

Abigail Gligor Research Assistant, Legacy Research Institute

High-Fat Diet and Acute Stress Have Different Effects on Object Memory During Adolescence and Young Adulthood

High-fat diet and acute stress have different effects on object memory during adolescence and young adulthood. Glushchak, Karina1; Ficarro, Alexandria1; Schoenfeld, Timothy J1. 1 Belmont University, Department of Psychological Science and Neuroscience. Feeding of a high-fat diet (HFD) during adolescence produces stronger impairments to learning and memory during adolescence than adulthood, however few studies directly examine the recovery of memory function from adolescent diet. In addition, many tests of learning and memory are confounded by either aversive or food-based stimuli, making it difficult to determine baseline memory processing affected by HFD. Thus, we utilized three cohorts of rats (adolescent HFD, young adult HFD, and adolescent HFD with recovery) to determine the effects of HFD at different time points on both object recognition and object location memory, dependent on the perirhinal cortex and hippocampus, respectively. To isolate stress as a variable, memory was tested at baseline or with acute cold water swim after object acquisition in all cohorts. Results show that novel object recognition is impaired by acute stress across all groups, but HFD alone only impairs object recognition memory during adolescence, when tested immediately. After a period of recovery, object recognition memory recovers following adolescent HFD. In addition, object location memory is impaired by HFD in all age groups and fails to recover from adolescent HFD following a recovery period. Together the data suggest that hippocampus-dependent behaviors are more resistant to acute stress across all ages and that perirhinal cortex-dependent behaviors are more resistant to HFD, except during the adolescent period. These results support that the adolescent period may be unique in long-lasting dysfunctions of HFD on hippocampal behaviors. This work was supported by an Undergraduate Research Grant by Psi Chi International Honors Society in Psychology.

Speaker

Karina Glushchak Undergraduate Student Researcher, Belmont University

The role of neuronal ensembles in extinction of oxycodone seeking

The role of neuronal ensembles in extinction of oxycodone seekingC. Gobin1, B. Sortman1, and B. Warren1, Department of Pharmacodynamics, University of Florida1The context and cues paired with drug self-administration become powerful indicators of drug availability that can induce craving and relapse. One possible strategy to prevent relapse is to reduce the strength of drug-stimuli associations through repeated presentation of the drug-associated cues while omitting the drug reward, referred to as extinction. Self-administration and extinction memories are thought to be encoded in the brain by patterns of neurons selectively activated by cues and reinforcers, called neuronal ensembles. We recently found that functionally distinct neuronal ensembles in the ventral medial prefrontal cortex (vmPFC) mediate self-administration and extinction of cocaine seeking. Here, we tested the hypothesis that distinct neuronal ensembles in the vmPFC mediate self-administration and extinction of oxycodone seeking. We trained adult male and female transgenic Fos-LacZ rats to lever press for oxycodone under an increasing FR schedule of reinforcement (three days each at FR1, FR2, and then FR3). We then put rats through 1 week of extinction or home-cage abstinence. We used the Daun02 inactivation procedure to selectively inactivate the Fos expressing ensembles associated with recall of drug seeking or extinction memories. Two days later, we tested rats' recall of oxycodone self-administration. We find that Daun02 inactivation of the putative oxycodone self-administration ensemble reduced oxycodone-seeking, while Daun02 inactivation

of the extinction ensemble was unaffected. Our findings suggest that vmPFC neuronal ensembles mediate self-administration but not extinction of oxycodone seeking.Funding source: NIDA Grant No. 4R00DA042102-02 awarded to BW and PA-18-906 awarded to CG

Speaker

Christina Gobin Postdoctoral research associate, University of Florida

Behavioral and Electron Microscopic Study of the Effects of Prolonged Loud Noise in Adult male Wistar Rats

Behavioral and Electron Microscopic Study of the Effects of Prolonged Loud Noise in Adult male Wistar RatsNino Gogokhia1, Mzia Zhvania1,2, Nadezhda Japaridze1,31Ilia State University, 2I. Beritashvii Experimental Center of Biomedicine, 3New Vision UniversityNoise pollution is associated with behavioral and neurological disorders. The disturbances provoked by noise can be better explained as the deficiencies of different functional networks. Auditory brain regions are not the only one structures that contribute to the processing of auditory signals. As our understanding of the effects of noise on auditory brain advances, the studies of noise consequences outside of classical auditory areas become of special importance. It is also notable that to date very few studies have been examined to determine the effects of prolonged noise on brain morphology in animals that have been behaviorally tested. Present behavioral and electron microscopic study was performed on adult male Wistar rats. The goal was to assess the effects of prolonged loud noise on learning, emotional state, locomotor activity and the ultrastructure/presynaptic architecture of hippocampal CA1 area and nucleus caudatus. The animals were exposed to 100 dB acoustic white noise for one hour per day, for a total of 10 consecutive days. Behavioral and ultrastructural studies were performed on the next day after 10-day exposure to noise. Learning was assessed in radial arm maze, locomotor activity '" in open field, emotional sphere - in cross-maze and open field. The results revealed significant noise effect on locomotor activity and emotional sphere. Ultrastrucutural alterations were identified in both regions of the brain but hippocampus was the most changed. The alterations were mostly mild and reversible. Thus, moderate chromatolysis of some neurons, mild destruction of components of protein synthesis apparatus, activation of glia and apoptosis of few neurons were observed. Quantitative EM analysis revealed alterations in the number of presynaptic mitochondria, total number of synaptic vesicles and the number of vesicles from different pools. Overall, the data indicate that even relatively short and intermittent loud noise provokes mild adverse effect on the behavior and fine structure of limbic and extrapyramidal areas of rat brain.Funded by: Shota Rustaveli National Science Foundation PhDF-18-1136

Speaker

Nina Gogokhia MD MClSc PhDs Neuroscience Researcher PhDs, LEPL I. Beritashvili Center of Experimental Biomedicine

Retrieval-extinction using novel information

Retrieval-extinction using novel information. Gonzalez, Angela 1,2, Wingert, Jereme 1, Sorg, Barbara 1,2. 1 Legacy Research Institute, Portland, OR, 2 Washington State University, Vancouver, WA.
Established memories can be modified during the reconsolidation time window by incorporating new and relevant information into an existing memory. Moreover, memory integration usually occurs when a prediction based on prior memory creates an error (a mismatch between what is expected and what is received). Current studies have targeted maladaptive memories using reconsolidation-based mechanisms like retrieval-extinction, a paradigm that incorporates extinction learning during the reconsolidation vulnerability window. We attempted to update a cocaine self-administration memory by presenting novel information during a retrieval session followed by extinction. Male rats were trained for 2 hr sessions for 14 days on a fixed-ratio 1 (FR1) schedule and then given a 30 min memory retrieval during which cocaine was received on an FR1 or variable ratio 5 (VR5) schedule- the latter was given to induce a prediction error. One

hour later, rats underwent a 190 min extinction session during which lever pressing had no consequences and the next day were tested for cue reinstatement. Three additional control groups received either no retrieval (No Retrieval) or an FR1 or VR5 retrieval but no extinction (No Extinction groups). We hypothesized that a VR5 vs. FR1 retrieval would be required to incorporate extinction learning and subsequently diminish cue reinstatement. Contrary to our hypothesis, VR5 retrieval did not reduce lever pressing during cue reinstatement compared with FR1 retrieval and No Retrieval groups and responding was similar to both No Extinction groups. These findings suggest that memory retrieval using a predictable (FR1) but not an unpredictable (VR5) contingency allows for integration of extinction learning into the original memory and that the VR5 retrieval may have protected the original 'œFR1 memory' from extinction. Funding: Alcohol and Drug Abuse Research Program (ADARP) award, Washington State University, Pullman, WA

Speaker

Angela Gonzalez PhD Student, Legacy Research Institute

Transcranial laser stimulation in behavioral neuroscience: theory, methods and applications

Transcranial laser stimulation in behavioral neuroscience: theory, methods and applications.Francisco Gonzalez-Lima, University of Texas at Austin. We will introduce transcranial infrared laser stimulation as a novel noninvasive method of brain stimulation with applications to the field of behavioral neuroscience. This presentation will build upon a body of recent evidence demonstrating that red-to-near infrared lasers can increase cytochrome oxidase activity and brain oxygenation, which improve behavioral outcomes and memory in animal models and humans. This exciting new method uses photonic energy from laser light that penetrates to the brain to photo-oxidize cytochrome oxidase and up-regulate oxidative energy metabolism. The primary mechanism consists of transcranially exposing the brain to a low-power, high-density source of luminous energy that delivers photons to the mitochondrial respiratory enzyme cytochrome oxidase, the main intracellular photon acceptor at the red-to-near-infrared wavelengths of light. Given the crucial role of energy metabolism for brain function, this type of brain stimulation can enhance behavioral, neurocognitive, and neuroprotective functions. Infrared lasers deliver light doses that are safe (too low in power to cause significant heat or any tissue damage), yet high enough in energy density to modulate neuronal functions. However, this intervention has not been widely adopted in spite of safe, portable, effective, and promising outcomes from animal and human studies. For the first time, the talks in this symposium will integrate brain and behavioral effects of transcranial laser stimulation from animal and human studies. We will summarize the state-of-the-science and potential of transcranial laser stimulation in behavioral neuroscience. We will demonstrate how animal models made possible the characterization of molecular, cellular, and regional brain systems and behavioral mechanisms, and how to translate these discoveries to human studies aimed to improve learning, memory and neuroprotection. This research is supported by grants from the Oskar Fischer Fund, Elhapa Foundation and NIH BRAIN initiative grants to PI Francisco Gonzalez-Lima and his group.

Speaker

Francisco Gonzalez-Lima Professor, Departments of Psychology, Psychiatry, Pharmacology/Toxicology, and Institute for Neuroscience, University of Texas at Austin

Estradiol activation of dorsal hippocampal TrkB occurs independently of increased mBDNF expression and is required for enhanced memory consolidation in female mice

Estradiol activation of dorsal hippocampal TrkB occurs independently of increased mBDNF expression and is required for enhanced memory consolidation in female miceKellie S. Gross 1, Randie L. Alf 1, Tiffany R. Polzin 1, Karyn M. Frick 11 Department of Psychology, University of Wisconsin-Milwaukee, Milwaukee, WI 53211 USA.The potent estrogen 17Î²-estradiol (E2) is known to enhance hippocampal memory and plasticity, however the molecular mechanisms underlying these effects remain unclear. Brain derived

neurotrophic factor (BDNF) and its receptor tropomyosin receptor kinase B (TrkB) are regulated by E2, but whether neurotrophic signaling is required for E2-induced enhancement of memory is unknown. Here, we examined the role of hippocampal TrkB signaling on E2-induced enhancement of memory consolidation in the object placement and recognition tasks. Bilateral infusion of the TrkB antagonist ANA-12 into the dorsal hippocampus of ovariectomized female mice immediately following object training blocked E2-induced enhancement of memory consolidation, supporting a role for TrkB-mediated signaling in estrogenic regulation of memory. Although E2 infusion increased levels of phospho-TrkB and mature BDNF (mBDNF) in the dorsal hippocampus within 4-6 hours, E2-induced increases in hippocampal mBDNF expression were not required for hippocampal TrkB activation and were not inhibited by TrkB antagonism. Therefore, E2 appears to regulate TrkB signaling to facilitate memory consolidation in a manner independent of mBDNF expression. Together these results provide the first direct evidence that E2 modulation of hippocampal TrkB signaling is required for its facilitative effects on memory consolidation and provide insight into the complex regulation of TrkB/BDNF signaling by E2 in the hippocampus.Funding: This work was supported by the National Institutes of Health (R01MH107886, F32MH118782, 2R15GM118304-02), the University of Wisconsin-Milwaukee Office of Undergraduate Research, and the University of Wisconsin-Milwaukee College of Letters and Science.

Speaker

Kellie Gross Postdoctoral Fellow, University of Wisconsin-Milwaukee

Ejaculation during mating facilitates social fear extinction in male mice.

Ejaculation during mating facilitates social fear extinction in male mice.
Cindy P. Grossmann1, Rohit Menon1, Christopher Sommer1, and Inga D. Neumann1
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Department of Neurobiology and Animal Physiology, University of Regensburg, Regensburg, Germany
Social Anxiety Disorder (SAD) is characterized by a persistent and intense fear of social situations. Current treatment options for SAD are rather unspecific and combine pharmacotherapy (e.g. benzodiazepines and/or antidepressants) with cognitive-behavioral therapy leading to gradual fear extinction. In this context, our lab has developed the social fear conditioning (SFC) paradigm, which allows us to induce specifically social fear in mice without affecting general anxiety- or depression-like behaviors. Using this paradigm, we have shown that the neuropeptide oxytocin (OXT), well-known for its pro-social and anxiolytic effects, reverses social fear in male and female mice. More precisely, a particular involvement of OXT has been identified into the lateral septum (LS). In males, an endogenous central release of OXT occurs acutely during mating, which has been linked with anxiolysis in rats. We aimed to investigate, how sexual behavior in male mice modulates fear and anxiety, focusing on the involvement of the neuropeptide OXT by combining behavioral, microdialysis, and pharmacological techniques as well as neuronal activity assessment. Our results showed that mating prior SFC extinction induced a facilitation of the extinction only if an ejaculation has occurred during mating. No effect of mating with or without ejaculation could be found on the extinction of non-social (cued) fear. Both mating with and without ejaculation induced a decrease in anxiety-like behavior. Microdialysis during mating revealed a specific release of OXT within the LS. However, a blockage of the OXTR with a specific antagonist infusion before mating could not reverse the effect of ejaculation on social fear extinction.
This project is supported by the DFG grant GRK2174.

Speaker

Cindy Grossmann PHD Student, Universität Regensburg

Understanding adolescent vulnerability to methamphetamine use disorder: the role of early life adversity, genes and cognition

Understanding adolescent vulnerability to methamphetamine use disorder: the role of early life adversity, genes and cognition

Alexandre A. Guerin 1,2; Katherine D. Drummond 1,2; Yvonne Bonomo 2,3; Kiymet Bozaoglu 4; Andrew J. Lawrence 1,2; Susan L. Rossell 3,5; Jee Hyun Kim 1,2

1 Florey Institute of Neuroscience and Mental Health
2 University of Melbourne
3 St Vincent's Hospital Melbourne
4 Murdoch Children's Research Institute
5 Swinburne University of Technology

Among illicit substances, methamphetamine represents one of the greatest global health threats. More alarming, people have reported using meth as early as 15 years of age. This is a major concern as adolescence is a period of heightened vulnerability to addiction. Evidence suggests that childhood adversity, cognitive deficits, and gene polymorphisms may be contributing factors. To investigate these factors, we recruited 35 current meth users (last use within 7 days) with a DSM-5 diagnosis of meth use disorder, and 35 matched-controls. Participants were administered the Childhood Trauma Questionnaire, the Barratt Impulsiveness Scale, and a cognitive task battery assessing cognitive flexibility and inhibitory control. Inhibitory control was also assessed using a novel cue reactivity task that we developed consisting of the pseudo-randomized presentation of meth-related cues counterbalanced with food-related cues. Whole blood was collected to assess polymorphisms in key addiction-related genes. Linear regression analyses revealed that performance in the cognitive flexibility and inhibitory control tasks were positively associated with age of onset of meth use (p's<0.05), but not length or severity of use. Poor inhibitory control in people who started using meth in adolescence was associated with childhood trauma (p=0.002). Preliminary chi-square analyses of addiction-related polymorphisms revealed that the Thr98Ser variant of the vesicular monoamine transporter 1 gene is more frequent in people who started using meth in adolescence (p=0.046). Overall, our results suggest that impaired inhibition during adolescence may be a risk factor that perpetuates meth use after experimentation and may in part contribute to the development of meth use disorder later in life. In addition, childhood adversity and gene polymorphisms may worsen inhibitory control deficits if meth use occurs in adolescence.

Funding Acknowledgement: Florey Foundation SupportNHMRC Career Development Fellowship (JHK)

Speaker

Alexandre Guerin PhD Candidate, The Florey Institute of Neuroscience and Mental Health

How oxytocin and vasopressin influence the making and breaking of family bonds

How oxytocin and vasopressin influence the making and breaking of family bondsAuthorsCaleigh D. Guoynes, Catherine A. MarlerAuthors' AffiliationUniversity of Wisconsin-Madison, PsychologyResearchCritical questions in the fields of neuroscience and animal behavior are how social groups are formed, how they are maintained, and how they are broken down. Oxytocin and vasopressin are neuropeptides involved in social behavior and have been shown to have critical roles in socio-sexual and parental bond formation. Less understood are the roles that oxytocin and vasopressin play in bond maintenance and breakdown. Of particular interest are monogamous species that simultaneous maintain a socio-sexual bond while forming and breaking parental bonds with successive litters of offspring. The extent to which parent and offspring behavior contribute to offspring dispersal and the role of hormones in this process is not understood. Here, we use the strictly monogamous and biparental California mouse to examine the role oxytocin and vasopressin in juvenile preference for their parents. Juveniles were given a preference test that included a chamber with their parents, a chamber with novel peers (one male, one female), or an empty chamber. We found that most juvenile California mice have a preference for their parents and spend more time with peers over the empty chamber. In males, oxytocin enhances juvenile social preference for their parents. Oxytocin does not influence social preference in females in this context. Vasopressin did not alter social preference for either females or males. Neither oxytocin nor vasopressin influenced behavior on the elevated plus or a novel object task, suggesting effects are specific to social behavior. Together, these results suggest that oxytocin in juvenile males promotes the parent-offspring bond maintenance and may inhibit peer socialization and dispersal.Funding AcknowledgementNSF-

1355163

Speaker

Caleigh Guoynes PhD Candidate, University of Wisconsin, Madison

The Bed Nucleus Stria Terminalis as a Mediator of Stress Resilience

The Bed Nucleus Stria Terminalis as a Mediator of Stress ResilienceAnand Gururajan 1, Gerard M Moloney 2, Ana Paula Ventura Da Silva 2, Timothy G. Dinan 2, John F. Cryan 2.1 University of Sydney, Australia2 University College Cork, IrelandStress resilience and stress susceptibility are traits which lie at opposing ends of the spectrum of response to chronic life stressors such as psychosocial trauma. This dichotomy in response is underscored by divergent neuromolecular changes in key brain regions which regulate the activation of the neuroendocrine system response and include the prefrontal cortex, hippocampus and the amygdala However, these limbic structures do not directly project to the paraventricular nucleus (PVN), a structure which releases corticotropic release factor (CRF), the molecular trigger for activation of the hypothalamic-pituitary-adrenal. Rather, they project to relay structures like the bed nucleus stria terminalis (BNST) which in turn sends afferents to the PVN to modulate CRF secretion. Thus, as a focal point, the BNST is uniquely positioned to gate or '˜fine-tune' the response to stress and may play an unexplored, critical role in determining whether an individual is stress-resilient or stress-susceptible. In this study, we used RNA-seq to examine the transcriptional profile of the BNST in adult, male mice that were classified as susceptible or resilient following a chronic psychosocial defeat stress paradigm. Using a bioinformatics pipeline on Galaxy, we carried out differential gene expression analysis (DEG) using DESeq2 and differentially exon expressed analysis (DEE) using DEXSeq. We then identified overlaps in these two datasets. In susceptible mice, the expression of 188 exons for 104 genes was significantly altered whereas in resilient mice, the expression of 87 exons for 71 genes was significantly altered. Gene ontology analysis revealed that in resilient mice, exons/genes for Lzts2, Nkd1, Sostdc1 and Bicc1 were associated with the negative regulation of the Wnt signalling pathway which has been implicated in depression. Future studies to investigate their functional roles in the BNST will provide novel insights into the molecular basis of stress resilience. AG was supported by Marie-Sklowdowska Actions Individual Fellowship during this study.

Speaker

Anand Gururajan Research Fellow, University of Sydney

Role of BNST CRFR1 receptors in incubation of fentanyl seeking

Role of BNST CRFR1 receptors in incubation of fentanyl seekingUtsav Gyawali 1, David A. Martin 1, Agnieszka Sulima 2, Kenner C. Rice 2, Donna J. Calu 11 Department of Anatomy & Neurobiology, University of Maryland, Baltimore, MD, USA2 NIDA, NIAAA Intramural Research ProgramThe time-dependent increase in cue-induced opioid seeking, termed '˜incubation of opioid craving', is modeled in rodents by examining responding for opioid-associated cues after a period of abstinence. With opioid drugs, withdrawal symptoms may heighten cue reactivity by recruiting brain systems involved in both reward-seeking and stress. Corticotrophin releasing factor (CRF) in the bed nucleus of the stria terminalis (BNST) is a critical driver of stress-induced relapse to drug seeking. Here, we sought to determine whether BNST CRF receptor 1 (CRFR1) signaling drives incubation of opioid craving in opioid-dependent (D) and non-dependent (ND) rats. First, we tested whether BNST CRFR1 signaling drives incubation of opioid craving in rats with short access fentanyl self-administration (SA). On Day 1 of forced abstinence, we gave bilateral intra-BNST vehicle injections to all rats and measured lever responding for opioid cues in absence of fentanyl infusions. On Day 30 of forced abstinence, we gave an identical test after bilateral intra-BNST injections of vehicle or CRFR1 receptor antagonist, R121919. Vehicle treated rats showed greater responding for opioid associated cues on Day 30 relative to Day 1, and this incubation effect was prevented by intra-BNST R121919 on Day 30. Next, we incorporated an opioid-dependence procedure to test whether BNST CRFR1 signaling drives

opioid cue-reactivity to a greater extent in D relative to ND rats. We trained rats to self-administer fentanyl for 5 days before initiating the dependence phase and resuming daily fentanyl SA sessions for 10 days. We gave intra-BNST R121919 or vehicle injections before testing during acute (Day 5) or protracted (Day 30) withdrawal. During acute withdrawal, antagonizing BNST CRFR1 decreased the number of press bouts and increased the inter-bout interval. Together, these findings suggest a role for BNST CRFR1 signaling in driving cue-reinforced opioid seeking after periods of forced abstinence.McKnight Memory and Cognitive Disorders Award (DJC), a NARSAD Young Investigator Grant #24950 (DJC), a NIDA grant R01DA043533 (DJC), the Department of Anatomy & Neurobiology at the University of Maryland, SOM & NIDA, NIAAA IRP

Speaker

Utsav Gyawali University of Maryland School of Medicine

The Effects of Adolescent Chronic Mild Stress on Female Wistar-Kyoto Rats

The Effects of Adolescent Chronic Mild Stress on Female Wistar-Kyoto Rats Anna Hallowell1, Elizabeth Sahagun2, Brent Bachman1, Kimberly P. Kinzig21Department of Biological Sciences; 2Department of Psychological Sciences, 1,2Purdue University, West Lafayette, INMood disorders are common and symptomatically challenging illness to treat. Despite years of research to understand underlying mechanisms and develop more effective treatment approaches, numerous challenges exist. There are many chronic stress models used to study mood disorders, however the majority have been developed with adult males. This is problematic considering that affective disorders are more common in women, and generally develop particularly during late adolescence. Additionally, studies have shown that there are fundamental behavioral, physiological, and neural differences between males and females in response to the same external stressors, furthering a need to develop sex-specific paradigms to accurately model the etiology of mood disorders in females. The Wistar-Kyoto (WKY) rat strain is a promising model. It is known to demonstrate endogenous hormonal and behavioral abnormalities that many symptom-presenting patients with depression exhibit. In this study, we test stress susceptibility of female WKY rats by using a three-week chronic mild stress (CMS) paradigm during late adolescence (days 45-66). We hypothesize that female WKY rats that undergo CMS will develop depressive-and anxiety-like characteristics that are typically not observed in a Wistar strain (CTL). To test this, body weight, food intake, body composition, and corticosterone levels throughout CMS are determined to evaluate physiological effects of stress. Immediately following CMS, animals undergo behavioral assessments of helplessness, anxiety, anhedonia, and locomotor activity to evaluate the development of mood disorder phenotypes. These tests are repeated during late adulthood (~ day 90) to determine whether expected stress-induced behavioral deficits persist later in life. The validation and characterization of this sex- specific model of mood disorders allows for more studies on the underlying mechanisms driving these disorders and ultimately contribute to the development of novel therapeutic strategies.

Speaker

Anna Hallowell Undergraduate Student Researcher, Purdue University West Lafayette

Cocaine and amphetamine regulated transcript (CART) signalling in the central nucleus of the amygdala modulates stress-induced alcohol seeking.

Cocaine and amphetamine regulated transcript (CART) signalling in the central nucleus of the amygdala modulates stress-induced alcohol seeking. Hand, Alexandra; Campbell, Erin; Letherby, Bethany; Huckstep, Katherine; Lawrence, Andrew; Walker, Leigh. The Florey Institute of Neuroscience and Mental Health, Parkville, Australia. The central nucleus of the amygdala (CeA) is a key hub regulating alcohol and stress interactions, however the exact neuronal populations that govern this interaction are not well defined. Here we examine the neuropeptide cocaine and amphetamine regulated transcript (CART) within the CeA in stress-induced alcohol seeking. We found that CART cells are predominantly expressed in the

capsular/lateral division of the CeA and are a subpopulation of protein kinase CÎ´ (PKCÎ´) cells, distinct from corticotrophin releasing factor (CRF)-expressing cells. Both stress (yohimbine) and stress-induced alcohol seeking activated CART cells in the CeA, while neutralisation of endogenous CeA CART signalling attenuated stress-induced alcohol, but not sucrose seeking. Further, intra-CeA exogenous CART peptide administration did not drive alcohol seeking. Consistent with this, blocking CART signalling within the CeA did not alter the motivation to obtain and consume alcohol, but did attenuate stressor-induced anxiety-like behaviour during abstinence from alcohol. Together, these data identify CeA CART cells as a subpopulation of PKCÎ´ cells that influence stress x alcohol interactions and mediate stress-induced alcohol seeking behaviours.

Speaker

Lexi Hand Master's Student, The Florey Institute of Neuroscience and Mental Health

Stress during puberty exerts sexually dimorphic effects on antidepressant-like behaviour and monoamine neurotransmitters in adolescence and adulthood

Stress during puberty exerts sexually dimorphic effects on antidepressant-like behaviour and monoamine neurotransmitters in adolescence and adulthood.ErinHarris 1, FranciscaVillalobos-Manriquez 2,3, GerardClarke 2,3,4, OliviaO'Leary 1,2. 1 Dept. of Anatomy & Neuroscience, 2 APC Microbiome Ireland 3. Dept. of Psychiatry and Neurobehavioural Science 4 INFANT Centre, University College Cork.Stress is a major risk factor for the development of major depression. Depression is twice as prevalent in women compared to men and this difference only emerges after puberty, suggesting that puberty may be a sensitive period during which sex-dependent vulnerability to depression might become established. However, no studies have yet investigated whether stress occurring specifically during the pubertal window is responsible for this sex difference in depression vulnerability. Thus, in this study, male and female rats were exposed to a three-day stress protocol during puberty (postnatal days 35-37 in females, 45-47 in males) and underwent behavioural tests in adolescence or adulthood measuring anhedonia, anxiety, locomotor activity and antidepressant-like behaviour. Pubertal stress reduced antidepressant-like behaviour in the forced swim test. Interestingly, this effect was manifested via different behavioural strategies in a sex-dependent manner. Pubertal stress decreased climbing behaviour in adolescent males and decreased swimming behaviour in adolescent females. However, in adults, only climbing was decreased in both sexes while swimming was unaffected. Previous studies have implicated monoaminergic signaling in forced swim test behaviours. We found that pubertal stress had a sexually dimorphic impact on dopamine and serotonin neurotransmitter concentrations in the brainstem. Pubertal stress did not impact anhedonia, anxiety, and locomotor activity at either age. However, we found significant sex differences in all behavioural tests, which further emphasizes the importance of studying both sexes. Taken together, these data suggest that stress during puberty exerts sex-specific effects on antidepressant-like behaviour possibly through discrete neurotransmitter systems. This project is funded by the Health Research Board, ILP-POR-2017-033.

Speaker

Erin Harris Postdoctoral researcher, University College Cork

Titrating synapse number to treat MDD in Fragile X Syndrome

Titrating synapse number to treat MDD in Fragile X Syndrome Chelcie F. Heaney1,2, Sanjeev V. Namjoshi1, Ayse Uneri1, Eva C. Bach1,2, Jeffrey L. Weiner1,2, Kimberly F. Raab-Graham1,2*. Affiliations:1Department of Physiology and Pharmacology, Wake Forest University Health Sciences, Medical Center Boulevard, Winston-Salem, NC 27157, USA 2 Wake Forest Translational Alcohol Research Center (WF-TARC), Wake Forest University Health Sciences, Medical Center Boulevard, Winston-Salem, NC 27157, USAAbstract: Rapid antidepressants are novel treatments for major depressive disorder (MDD) and work by blocking N-methyl-aspartate receptors (NMDAR), which, in turn, activate the protein synthesis pathway regulated by

mechanistic/mammalian target of rapamycin complex 1 (mTORC1). Our recent work demonstrates that the RNA-binding protein Fragile X Mental Retardation Protein (FMRP) is downregulated in dendrites upon treatment with a rapid antidepressant. Here, we show that the behavioral effects of the rapid antidepressant Ro-25-6981 require FMRP expression and Ro-25-6981 treatment promotes differential mRNA binding to FMRP in an mTORC1-dependent manner. Further, we identified that these mRNAs regulate transsynaptic signaling. Using a novel technique, we show that synapse formation underlying the behavioral effects of Ro-25-6981 require GABABR-mediated mTORC1 activity in WT animals. Finally, we demonstrate that in a clinically relevant animal model of Fragile X Syndrome (FXS), which lacks FMRP expression, GABABR activity is detrimental to the effects of Ro-25-6981. These effects are rescued when GABABRs are blocked in addition to treatment with Ro-25-6981, indicating that rapid antidepressants alone may not be an effective treatment for people with FXS and MDD.Funding: CFH (NIH/NIAAA T32 AA007565), KRG (NSF IOS 1026527 NIH R01 AA026551, NIH P50 AA025117, DoD USAMRMC W81XWH-14-1-0061).

Speaker

Chelcie Heaney Postdoctoral Research Fellow, Wake Forest School of Medicine

Behavioral profile of a hallucinogenic compound 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine in rats

Behavioral profile of a hallucinogenic compound 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine in ratsHerian Monika1, Skawski Mateusz1, Wojtas Adam1, Sobocińska Małgorzata1, González-Marín Alejandro 1, Noworyta-Sokołowska Karolina2, Gołembiowska Krystyna1. 1Department of Pharmacology, Maj Institute of Pharmacology, Polish Academy of Sciences, Smętna Str. 12, 31-343, Kraków, Poland. 2Affective Cognitive Neuroscience Laboratory, Maj Institute of Pharmacology, Polish Academy of Sciences, Smętna Str. 12, 31-343, Kraków, Poland4-Iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine (25I-NBOMe) is an iodine representative of synthetic hallucinogens' group – NBOMes. It exhibits a high binging affinity mainly for 5-HT2A/C serotonin receptors being their potent agonist. 25I-NBOMe is known to alter perception and mood in human. The aim of this study was to investigate the effect of acute and chronic injections of 25I-NBOMe on hallucinogenic properties, motor activity, cognitive functions and anxiety induction in rats. The drug was administered in the dose of 0.3 mg/kg (sc) acutely or subchronically for 7 days. Hallucinogenic activity was assessed in the Wet Dog Shake (WDS) test, motor activity was measured in the Open Field (OF) test, short-term memory in the Novel Object Recognition (NOR) test and anxiety was evaluated in the Light/Dark Box (LDB) test. 25I-NBOMe was found to evoke hallucinogenic activity after single injections and induce tolerance after multiply administration. Motor activity was decreased in both cases, while repeated injections caused stronger depression of rats' locomotion. Single injection did not alter recognition pattern in NOR test, in contrast to multiply injections that influenced cognitive functions. 25I-NBOMe seemed to induce anxiety; however, subchronic injections increased rats' activity in the dark zone. Our results indicate that 25I-NBOMe affects motor and cognitive functions as well as elicits anxiety. Although decrease in hallucinogenic activity after repeated administration seems to result from 5-HT2A tolerance development, changes in locomotion, memory and anxiety induction may be mediated via other receptors apart from 5-HT2A receptor activation. Thus, 25I-NBOMe due to its agonist action at serotonin receptors exerts a profound impact on rats' behavior. The study was supported by the National Science Centre Grant no. 2016/21/B/NZ7/01131. MH acknowledges the support of InterDokMed project no. POWR.03.02.00-00-I013/16.

Speaker

Monika Herian PhD candidate, Maj Institute of Pharmacology, Polish Academy of Sciences

Time-restricted feeding from adulthood to old age improves biconditional associative learning in geriatric rats regardless of macronutrient composition

Time-restricted feeding from adulthood to old age improves biconditional associative learning in geriatric rats regardless of macronutrient compositionAbbi R. Hernandez1, Quinten P. Federico2, Sara N. Burke2 1Department of Medicine; Division of Gerontology, Geriatrics, and Palliative Care, The University of Alabama at Birmingham, Birmingham, AL, USA; 2 Department of Neuroscience and McKnight Brain Institute College of Medicine, University of Florida, Gainesville, FL, USA.Abstract: Declining health and cognition are hallmarks of advanced age that reduce both the quality and length of the lifespan. While caloric restriction has been highlighted as a dietary intervention capable of improving the healthspan through the restoration of metabolic function in late life, time-restricted feeding and changes in dietary macronutrient composition may be more feasible alternatives with similar health outcomes. To investigate the potential of these two interventions, a pilot cohort of fully mature adult male rats were placed on a time-restricted feeding regimen of a ketogenic or micronutrient and calorically matched control diet from 8 to 21 months of age. A third group of rats was permitted to eat standard chow ad libitum. At 22 months, all rats were then placed on time-restricted feeding at a 15% caloric deficit and tested on a biconditional association task. Regardless of dietary composition, time-restricted-fed rats performed significantly better than ad libitum-fed rats. This observation could not be accounted for by differences in motivation, procedural or sensorimotor impairments, indicating that mid-life dietary interventions capable of preventing metabolic impairments may also serve to prevent age-related cognitive decline. While the data presented here are preliminary (small sample size of 3-4/diet group), additional animals are currently undergoing the feeding regimen, and will be added into the behavioral studies at a later date. Acknowledgements of Funding: This work was supported by the National Institutes of Health, National Institute on Aging (RF1AG060977; 1F31AG058455).

Speaker

Abbi Hernandez

Contributions of gonadal hormones to intertemporal choice in male and female rats.

Contributions of gonadal hormones to intertemporal choice in male and female rats.Caesar M. Hernandez1,3, Alexa-Rae Wheeler1, Caitlin A. Orsini1,2, Tyler W. Ten Eyck1, Chase C. Labiste1, Noelle G. Wright1, Barry Setlow2,3, Jennifer L. Bizon1,3,Departments of 1Neuroscience, 2Psychiatry, 3McKnight Brain Institute, University of Florida, Gainesville FloridaIntertemporal choice involves decisions among options that differ in both reward magnitude and delay to reward delivery. All else being equal, individuals prefer large over small rewards; however, individuals tend to more readily choose small over large rewards the longer they must wait for the large reward (i.e., the value of the large reward is 'œdiscounted' by the delay to its delivery). Individual differences intertemporal choice can predict life outcomes such as educational attainment and socioeconomic status. Moreover, extreme preferences for either small, immediate rewards (greater 'œimpulsive choice') or large, delayed rewards (reduced impulsive choice) associate with psychiatric disorders. Gonadal hormones have been proposed to contribute to individual differences in intertemporal choice both within and between sexes, but relatively few studies have directly tested this hypothesis. The current study evaluated the contributions of estrogen and testosterone to intertemporal choice in male and female young adult rats. Young adult (4 mo.) male and female Fischer 344 ï‚´ Brown Norway F1 hybrid (FBN) rats were trained in an intertemporal choice (delay discounting) task in which they made discrete trial choices between levers that yielded a small, immediate reward (1 food pellet) vs. a large reward (3 food pellets) delivered after a delay period. The delays to large reward delivery increased in blocks of trials across each session (0, 10, 20, 40, 60 s delays). Rats were initially trained on the task, then divided into two groups matched for choice behavior that received gonadectomy or sham surgery. After recovery, rats were re-tested on the task, and data compared both between groups and before/after surgery. Relative to males, female rats displayed greater impulsive choice and delay intolerance. Castration caused an increase in choice of the small, immediate reward (increased impulsive choice) compared to both sham controls and pre-surgical baseline performance. Surprisingly, however, 5 days of subcutaneous injections of a physiological dose of testosterone (125 Âµg) in castrated rats did not reverse this phenotype, suggesting that the effects of castration on impulsive choice are not mediated solely by reductions in circulating testosterone. Considered together, these data demonstrate a role for testicular hormones in maintaining preference for large, delayed rewards, but that testosterone alone (at least under the conditions tested here) is not sufficient to reproduce this effect.

Speaker

Caesar Miguel Hernandez Postdoc Fellow, University of Alabama at Birmingham

Apathy as a loss of precision of prior beliefs about action outcomes: Evidence from Parkinsonâ€™s disease and noradrenaline.

Apathy as a loss of precision of prior beliefs about action outcomes: Evidence from Parkinson's disease and noradrenaline.Frank H Hezemans 1, Noham Wolpe 1, Claire O'Callaghan 1, Rong Ye 1, Catarina Rua 1, P Simon Jones 1, Alexander G Murley 1, Negin Holland 1, Ralf Regenthal 2, Kamen Tsvetanov 1, Luca Passamonti 1, James B Rowe 1. 1 University of Cambridge, 2 University of Leipzig.Apathy is a common and debilitating symptom in many diseases, including Parkinson's disease (PD), but its underlying mechanisms remain poorly understood. Cell loss in the locus coeruleus (LC) and the consequent noradrenergic depletion are thought to contribute to cognitive problems that characterize PD, including apathy. Noradrenaline (NA) is also thought to signal uncertainty of expectations about the environment. We propose a new model of apathy in the context of the Bayesian brain framework, where goal-directed behavior requires predictions of action outcomes to be held with sufficient precision for explaining away sensory input. We hypothesized that apathy results from reduced precision of priors for action, and that the relative weighting of priors is modulated by NA. We tested these hypotheses using Bayesian modeling of a visuomotor task that required effortful, goal-directed behavior. In a healthy cohort (N=47), individual differences in prior precision were negatively associated with trait apathy, suggesting that more apathetic individuals had less precise priors for action. We then tested PD patients (N=19) in a randomized, placebo-controlled, double blind, cross-over study with a single dose of 40mg atomoxetine. As a baseline measurement of LC integrity, patients underwent 7 tesla neuromelanin-sensitive magnetization transfer imaging. Individual differences in prior weighting were again negatively associated with patients' trait apathy. The effect of atomoxetine on prior weighting depended on LC signal, such that lower LC integrity was associated with a greater behavioral effect of atomoxetine. These results support a Bayesian account of apathy that could inform new stratified trials of NA-ergic therapies in selected PD patients.This study was supported by UK Medical Research Council; Wellcome Trust; Parkinson's UK; Cambridge Trust and Fitzwilliam College; James S. McDonnell Foundation 21st Century Science Initiative; NIHR Cambridge Clinical Research Facility.

Speaker

Frank Hezemans Visiting Student, University of Cambridge

Investigating USVs and tickle response in rat models of ID/ASD

Investigating USVs and tickle response in rat models of ID/ASD. R Hickson 1,2,3, S Till 1,2,3, S Brown 4,5, A Lawrence 4,5, P Kind 1,2,3. 1) Centre for Discovery Brain Sciences, University of Edinburgh 2) Simon's Initiative for the Developing Brain 3) Patrick Wild Centre 4) Scotland's Rural College (SRUC) 5) Roslin Institute, University of Edinburgh. Rats naturally live in large social groups and interact with a wide range of conspecifics throughout their lifetime. Ultrasonic vocalisations (USVs) serve important functions in social interactions, and alterations in production and/or perception of USVs have significant measurable impacts on social behaviour. During bouts of rough-and-tumble play, rats emit especially high rates of USVs. Heterospecific tickle stimulation mimics some aspects of rough-and-tumble play and has been used extensively to study USVs and affective state in rats. We used tickle to investigate USVs in rat models of neurodevelopmental disorders that are highly correlated with intellectual disability (ID), autism spectrum disorder (ASD) and impairments in social interaction and communication in humans. In a rat model of Fragile X Syndrome, we found comparable behavioural tickle responses, USV frequency distributions, and call characteristics to wild-type littermate controls. In contrast, two rat models of SYNGAP1 haploinsufficiency showed escape behaviour during tickling as well as differences in USV frequency distributions and call characteristics compared to wild-type littermate controls. Our preliminary results suggest that tickle may be an effective method for detecting social phenotypes in rat models of ID/ASD. Given that sensorimotor gating may be altered in ID/ASD, future work will investigate the effect of environmental conditions on tickle response. This work was supported by the Simons Initiative for the Developing Brain.

Speaker

Raven Hickson PhD Student, University of Edinburgh

Acoustic Vocalisation Early Response Technologies (AVERT)

Acoustic vocalisation early response technologies (AVERT)Liane Hobson, R. Sonia Bains, Simon Greenaway, Michelle Stewart, Patrick M. Nolan and Sara WellsMedical Research Council Harwell Institute, Harwell, Oxfordshire, OX11 0RDThe use of novel mouse models to study human disease poses serious challenges for the scientific community. Limitations in current phenotyping techniques can cause relevant phenotypic effects to be missed, especially if they are subtle and/or novel. Further, the early stages of disease can be difficult to study as disease onset is unpredictable. New strains can also have distinct, unknown, unpredictable welfare needs that must be addressed. Welfare checks typically consist of short, daily assessments of visual cues like hunching and grimacing. Whilst important, these checks may delay welfare interventions; issues can arise between checks and mice may hide signs of vulnerability, as they are a prey species. Recent advancements, like the home cage analysis system developed at MRC Harwell, enable longer recording periods and the identification of subtle, previously unknown phenotypes, so scientists can start to address these issues. However, further development of novel methods is necessary to overcome these challenges. Mice use ultrasonic vocalisations (USVs) in multiple social contexts, likely for communication. Accordingly, there is evidence that models of neurodegenerative diseases show changes in USVs that may correspond to communicative deficits in human patients. Vocal cues may also precede visual indicators of welfare concerns and disease onset. USVs could thus potentially be used to improve mouse welfare and to study the early stages of disease. USVs are currently poorly understood due to the expense of recording equipment, computational challenges and difficulties in reliably inferring their function. I am working closely with the phenotyping and informatics teams at MRC Harwell to overcome these challenges. We have developed a cost effective system that synchronously records USVs and behaviour over long periods. By linking these two traits, I will be able to infer the affective state of USVs. I am working with ethologists to ensure that links are reliable. I will discuss both the development of this technology and how we have begun to use it in initial investigations of the effects of life-stage on vocal activity in baseline strains of mice. Funding: NC3Rs training fellowship

Speaker

Liane Hobson nc3rs training fellow, MRC Harwell Institute

Sex- and age-specific roles of the amygdala and hippocampal subregions in fear-based cognitive bias in rats

Sex- and age-specific roles of the amygdala and hippocampal subregions in fear-based cognitive bias in rats. Travis E. Hodges 1, Sophia H. Noh 1, Grace Y. Lee 1, Liisa A.M. Galea 1. 1 Department of Psychology, University of British Columbia, Djavad Mowafaghian Centre for Brain Health, Vancouver, BC, Canada. Negative cognitive bias is an increased perception of neutral situations or objects as negative, and is a cognitive symptom of depression. Furthermore, negative cognitive bias can predict the onset of future depressive episodes in at-risk adolescent females. However, the underlying neural mechanisms of cognitive bias have seldom been investigated. Here, adolescent, young adult, and middle-aged adult male and female Sprague-Dawley rats underwent a fear-based cognitive bias task. Rats were trained for 16 days to distinguish between two contexts: a context paired with foot-shock and a context paired with no foot-shock. Two days after initial training (day 18), rats were tested for cognitive bias in response to an ambiguous context and coded for positive (low freezing) or negative (high freezing) cognitive bias. Adolescent rats displayed a positive bias, whereas young adult rats displayed a negative bias in response to the ambiguous context, regardless of sex. Curiously, in middle-aged adults, females displayed a more positive bias (less freezing) in response to the ambiguous context whereas middle-aged males displayed a negative cognitive bias. Sex differences in activation of the basal amygdala, lateral amygdala, central

amygdala, and of the subregions of the hippocampus (Fos-ir) in response to the ambiguous context in middle-aged rats were seen with negative correlations in males and positive correlations in females. Sex- and age-specific correlations between freezing behaviour and immature neurons in the hippocampus were also examined. Our data suggest a more optimistic cognitive bias in females than in males that emerges in older adulthood. A more optimistic cognitive bias is seen adolescence, regardless of sex, which may be driven by experience or hormone environment. Acknowledgements: CIHR MOP 142328 held by LAMG, IMH Marshall Fellowship held by TEH.

Speaker

Travis Hodges Postdoctoral Researcher, The University of British Columbia

Excitatory and Inhibitory Synaptic Markers in an Animal Model of Normal Age-Related Memory Loss

Excitatory and Inhibitory Synaptic Markers in an Animal Model of Normal Age-Related Memory Loss. David Horovitz1, Laura Askins1, Joseph McQuail1. 1University of South Carolina. Aging is characterized by decline of memory that depends on the hippocampus and increased risk for developing Alzheimer's disease (AD). Anomalous patterns of hippocampal activity are observed in prodromal AD wherein a shift in the excitatory-inhibitory (E/I) dynamic underlies memory deficits. Memory loss in normal aging, as opposed to AD, is not associated with loss of hippocampal neurons. Consequently, attention has shifted to examine hippocampal synapses in brain aging. E/I disruptions in the DG-CA3 network are proposed to underlie age-related deficits in spatial learning that may be ascribed to the dorsal, and not ventral, aspect of the hippocampus. These observations indicate that a neuroanatomically precise characterization of changes to excitatory and inhibitory synapses in the hippocampus of aging individuals could elucidate the circuit-basis of memory changes that confer increased risk for AD. We characterized young adult (6 mo) and aged (24 mo) male, F344Ã—BN-F1 hybrid rats for individual differences in spatial learning and used brains from these rats in histological analyses. Sections spanning the dorsal-ventral extent of the hippocampus were labelled using antibodies raised against VGluT1, a marker of glutamatergic synapses, and VGAT, a marker of GABAergic synapses, and visualized with secondary antibodies coupled to fluorescent dyes. Our analyses revealed marginal differences between young rats and aged rats rated as memory-unimpaired or memory-impaired. Post hoc comparisons suggest these differences are attributed to lower level of VGluT1 in dorsal and ventral CA3 between young rats and memory-impaired aged rats. Alternatively, correlational analyses applied across the full range of aged performance revealed a significant inverse relationship between spatial learning and VGAT-staining intensity in the dorsal CA3. Our preliminary analyses are consistent with our hypothesis that E/I disruption centered on CA3 is of special relevance to individualized decline of memory function in aging. Furthermore, these changes were consistently, though not exclusively, evident in the dorsal region of the hippocampus. Ongoing analyses in our lab are further differentiating among discrete synaptic layers to elucidate the circuit bases for these differences. NIH Grant K01AG061263 to JM.

Speaker

David Horovitz First Year Medical Student, University of South Carolina School of Medicine

The role of ventral subiculum M4 muscarinic receptors in alcohol seeking

The role of ventral subiculum M4 muscarinic receptors in alcohol seeking. Kate Huckstep 1, Leigh C Walker 1, Nicola Chen 1, Lexi J Hand 1, Andrew J Lawrence . 1The Florey Institute of Neuroscience and Mental Health, Parkville Australia. Alcohol Use Disorder (AUD) is a chronic relapsing disease, with limited therapeutic treatment options despite its large socioeconomic burden. Relapse propensity is a significant hurdle in AUD treatment. One trigger for relapse is returning to a context previously associated with alcohol. The ventral subiculum (vSub) has been implicated in the processing of contextual cues, with a projection from the vSub to nucleus accumbens shell (ACbSh) thought to mediate this role. M4 muscarinic

acetylcholine receptors (mAChRs) are expressed within the vSub, however, the distribution and role of M4 mAChRs within the vSub in relapse to alcohol seeking are unknown. Here, using our translationally relevant model of long-term alcohol consumption we first examined the regulation of vSub M4 mRNA, revealing a downregulation of Chrm4 expression (M4 mRNA) following long-term alcohol consumption/withdrawal. Next, to examine the expression of M4 receptors on vSub to AcbSh projection neurons, we combined retrograde tracing with RNAscope. Analysis revealed dense M4 mAChR expression, including on vSub neurons projecting to the AcbSh. Finally, we examined the functional role of M4 mAChRs in context-induced alcohol seeking, via administration of the M4 mAChR positive allosteric modulator (PAM), VU0467154. Systemic administration of VU0467154 (30mg/kg, p.o) significantly reduced ABA renewal of alcohol seeking in rats, but not when tested in the extinction context (ABB). Further, this was mediated in the vSub as Intra-vSub administration of VU0467154 (3 Î¼mol/ hemisphere) significantly reduced ABA, but not ABB renewal of alcohol seeking. Moreover, intra-vSub VU0467154 administration had no impact on locomotor activity, food or water consumption. Together our data suggest that long term alcohol consumption dysregulates the vSub, and that use of a PAM can prevent relapse. Thus, M4 mAChR allosteric modulation is a potential candidate for the treatment of AUD, and aspects of this are mediated in the vSub.

Speaker

Kate Huckstep Master's Student, Florey Institute of Neuroscience and Mental Health

Acute oral pretreatment with the mTOR inhibitor Everolimus blocks craving-related changes in prelimbic cortex protein expression

Acute oral pretreatment with the mTOR inhibitor Everolimus blocks craving-related changes in prelimbic cortex protein expression Laura L. Huerta Sanchez1, Alvin S. Chiu1, Matthew C. Kang1, Karen K. Szumlinski1,21Department of Psychological and Brain Sciences, 2Department of Molecular, Developmental and Cell Biology and the Neuroscience Research Institute, University of California Santa Barbara, Santa Barbara, CA, USACue-elicited drug-craving is a cardinal feature of addiction that intensifies and becomes resistant to extinction during protracted withdrawal. In a rat model, these addiction-related behavioral pathologies are mediated, respectively, by a time-dependent increase in PI3K/Akt signaling and reduced Group 1 metabotropic glutamate receptor (mGlu) expression within the ventromedial prefrontal cortex (vmPFC). Recently, we showed that single oral dosing with the FDA-approved mTOR inhibitor Everolimus (1.0 mg/kg) blocks incubated cocaine-seeking for a 24-h period in rats. Here, we examined the protein correlates of Everolimus' 'œanti-craving' effect within the prelimbic (PL) and infralimbic (IL) subregions of the vmPFC. Rats self-administered IV cocaine for 10 days during which each cocaine delivery was paired with a light-tone stimulus complex. At 3 or 30 days withdrawal, rats underwent a 2-h test for cue-reinforced responding, the vmPFC subregions dissected immediately upon test completion and immunoblotting conducted. Relative to rats tested in early withdrawal, cocaine-incubated rats exhibited increased expression of Homer2a/b and phosphorylated Akt, P70-rpS6 kinase, and rpS6, as well as decreased expression of the monomer and dimer forms of mGlu1 and mGlu5. No changes in Homer proteins or mGlu1/5 were apparent in the IL. Everolimus pretreatment either blocked or reversed all of the incubation-associated protein changes within the PL, without affecting protein expression in rats tested in early withdrawal. From these data we conclude that the ability of acute oral pretreatment with Everolimus to block incubated cocaine-craving reflects a normalization of mTOR/Akt/PI3K signaling, and consequent effects upon Homer2/mGlu function within the PL. Such data further Everolimus treatment as a viable strategy for interrupting cocaine-craving and facilitating addiction recovery during protracted withdrawal.Funding provided by a Faculty Research Grant from UCSB.

Speaker

Laura Huerta Sanchez Ph.D. Student, University of California, Santa Barbara

Using anxiety as a sex-specific neuropsychiatric biomarker of Alzheimer's disease.

Using anxiety as a sex-specific neuropsychiatric biomarker of Alzheimer's disease. Holly C. Hunsberger 1,2, Seonjoo Lee 3,4, Jiook Cha 2,5,6,7, Christine A. Denny 1,2. 1 Division of Systems Neuroscience, New York State Psychiatric Institute (NYSPI) / Research Foundation for Mental Hygiene, Inc. (RFMH), New York, NY, 2 Department of Psychiatry, Columbia University (CU), New York, NY, 3 Mental Health Data Science, NYSPI/RFMH, 4 Department of Psychiatry Biostatics, CU, 5 Division of Child and Adolescent Psychiatry, NYSPI/RFMH, 6 Data Science Institute, CU, 7 Department of Psychology, Seoul National University. Neuropsychiatric disturbances, such as depression and anxiety, are observed in 90% of Alzheimer's disease (AD) patients and are frequent in those at risk for AD. However, until recently, much of the research narrowly targeted co-morbid depression. Clinical reports have provided evidence that anxiety symptoms predict the conversion to AD, over and beyond the effects of depression, memory loss, and even atrophy. Similarly, epidemiological studies show that neurodegeneration and clinical symptoms occur more rapidly in females once diagnosed. To study how anatomical sex and anxiety impact AD progression, I used our activity-dependent tagging system, the ArcCreERT2 x (ChR2)-EYFP x AD (APP/PS1) mice. These mice allow for brain-wide indelible labeling of neurons activated during learning, which then can be compared with secondary neuronal ensembles activated during memory retrieval. The neurons activated at both time points represent a memory trace or engram. Here, we aimed to identify the neural ensembles linking anxiety and memory loss following AD progression by utilizing behavioral studies, calcium imaging and whole-brain microscopy, in female and male mice. We found: 1) Female AD mice exhibited anxiety-like behavior at an earlier age compared to controls and male mice, 2) AD female mice displayed memory deficits as early as 2 months of age, 3) Anxiety-like behavior correlated with memory impairment only in AD female mice, and 4) Unlike their male counterparts, female AD mice showed a decline in memory traces in the CA3 of the hippocampus. We are currently working to translate these findings to humans using the Alzheimer's disease neuroimaging initiative (ADNI) dataset. We have found that in humans, anxiety predicts transition to dementia and that anxiety has a sex-specific effect on brain atrophy. This project is supported by a K99/R00 award from the NIA.

Speaker

Holly Hunsberger Associate Research Scientist/Research Scientist III, Columbia University

A role for adult neurogenesis in a probabilistic learning task

A role for adult neurogenesis in a probabilistic learning task
Kathleen B. Huntzicker 1,2, Rosie-Marie Karlsson 1, Heather A. Cameron 1
1 National Institute of Mental Health, Bethesda, MD, USA
2 Brown University, Providence, RI, USA

Hippocampal adult neurogenesis has been implicated in the neural mechanisms for many complex behaviors, including stress response, attention, and reward motivation. In this study, we employ a pharmacogenetic method of neurogenesis ablation to study the role of newly-born hippocampal neurons in probabilistic learning without subjecting animals to injection or surgical stress. Rats expressing herpes simplex virus thymidine kinase (HSV-TK) are fed the anti-viral drug valganciclovir in adulthood to completely inhibit hippocampal neurogenesis. Treated GFAP-TK (TK) rats do not exhibit any deficits in many standard learning tasks. However, previous studies from our lab have found that TK rats show differential responses to ambiguous threat cues as well as decreased effort to gain rewards when compared to wild-type controls, two effects that may be linked to unpredictability inherent to those tests. In this study, we use an operant two-armed bandit task to study responses to ambiguous reward feedback. Rats are exposed to two levers, one of which produces a food reward pellet 80 percent of the time, and the other, 20 percent. This type of probabilistic learning ‴ and subsequent reversal learning when lever outcomes are switched ‴ provides many opportunities to study response to ambiguous feedback, as unexpected results can signal either a reversal or one of the low probability outcomes. In addition, by using outcome likelihoods that are probabilistic rather than deterministic, the paradigm is more translatable to human learning studies and more representative of situations in nature. We find that in one version of this task, male TK rats exhibit a higher win-stay ratio and earn more rewards than wild-type controls, suggesting that TK rats employ different strategies than WTs when seeking rewards under ambiguous conditions. An ongoing study investigates whether female TK rats exhibit similar strategies to their male TK counterparts, and future research will explore whether genotype differences still exist when outcome likelihoods are deterministic.

Together, our findings suggest a role for adult neurogenesis in explore-exploit decision-making and more generally in behavioral responses to situational uncertainty.

Speaker

Kathleen Huntzicker PhD Student, Brown University

Sex- and task-specific cognitive deficits in the Setd1a loss-of-function mouse model of schizophrenia risk

Sex- and task-specific cognitive deficits in the Setd1a loss-of-function model of schizophrenia riskSofiya Hupalo 1, Emily Alway 2, Kirsten P. Gilchrist 2, Joseph A. Gogos 3, David A. Kupferschmidt 2, Joshua A. Gordon 2,41. Postdoctoral Research Associate Training Program, National Institute of General Medical Sciences, Bethesda, MD2. Integrative Neuroscience Section, National Institute of Neurological Disorders and Stroke, Bethesda, MD3. Zuckerman Institute, Columbia University, New York, NY4. National Institute of Mental Health, Bethesda, MDAlthough cognitive deficits are a core symptom of schizophrenia, there are no approved procognitive treatments for the disease. Thus, there is a need to better understand the etiology and neurobiology of cognitive impairment in schizophrenia. Human genetic studies demonstrate that mutations in the SETD1A gene, a transcriptional regulator, confer a large schizophrenia risk. To identify neurobiological mechanisms contributing to cognitive dysfunction in this disease, the present studies assessed cognitive function in mice with a heterozygous loss-of-function mutation in the orthologous SETD1A gene. Male and female Setd1a+/- mice were tested in two tasks: a delayed non-match-to-sample test of spatial working memory and the 5-choice serial reaction time test (5-CSRTT) of attention. We observed that Setd1a+/- mice exhibit deficits in learning the working memory task as measured by days to reach task criteria. However, after reaching criteria, Setd1a+/- mice performed similar to wildtypes under conditions of high cognitive load (long delays). In contrast to working memory, Setd1a+/- mice learned the 5-CSRTT at rates similar to wildtypes. After task acquisition, animals underwent additional 5-CSRTT procedures aimed to increase attentional load. Preliminary data suggest that while Setd1a+/- males performed comparably to wildtypes under conditions of high attentional load (short stimulus duration), Setd1a+/- females performed with worse accuracy and committed more errors of omission. Additional studies are conducting multi-site neurophysiological recordings to assess neural synchrony associated with working memory performance in Setd1a+/- mice. These studies will characterize the neurophysiological profile in this model and will lead to the development of specific hypotheses regarding the pathophysiology of cognitive dysfunction which can be tested in individuals with SETD1A mutations and idiopathic schizophrenia.

Speaker

Sofiya Hupalo Postdoctoral Fellow, National Institutes of Health

Chronic adolescent stress induces a sex-specific, PTSD-like phenotype in adult rats predicted by electrodermal activity

Chronic adolescent stress induces a sex-specific, PTSD-like phenotype in adult rats predicted by electrodermal activityHyer, Molly M. 1; Howell, Paul 1; Burns, Choe M. 1; Dyer, Samya K. 1; and Neigh, Gretchen N. 11 Department of Anatomy and Neurobiology, Virginia Commonwealth University, Richmond, VA 23298Trauma exposure during vulnerable developmental periods, such as adolescence, increases risk for Post-Traumatic Stress Disorder (PTSD) in adulthood '" with women at considerably higher risk than men. In humans, elevated skin conductance measured following the traumatic incident are highly predictive of later PTSD manifestation. As developmental stress is a risk factor for PTSD, individuals with a stress history and that display elevated electrodermal reactivity following trauma, are a high-risk group for stress-induced psychiatric dysfunction. Here, we used an animal model of chronic adolescent stress that has previously been shown to induce long-lasting changes to psychiatric function to determine the extent to which stress

history interacts with sex to induce PTSD-like behaviors following fear conditioning in rats. Male and female rats were exposed to a mixed modality stress paradigm throughout adolescence (CAS) comprised of social defeat and physical restraint. In adulthood, acoustic startle response (ASR) was assessed in non-stressed (NS) and CAS rats over six days: baseline, fear-conditioning, fear-potentiated startle, fear extinction training, and safety learning. Electrodermal response was collected at baseline as well as following fear conditioning and safety learning using eSense skin response sensors. Following fear conditioning, CAS males displayed a higher ASR compared to controls. While both CAS males and females displayed extinction learning similar to controls, CAS females maintained an elevated ASR through the safety learning day. This behavior positively correlated with skin conductance taken after fear-conditioning. Taken together, these data indicate that CAS heightens reactivity to trauma (fear-conditioning), however, sex determines whether or not this behavior is maintained. In females, elevated electrodermal activity following fear-conditioning is predictive of impaired extinction behavior, suggestive of a PTSD-like phenotype. These findings suggest that skin conductance may be a useful predictor of stress-induced disorders in females, along with ASR, allowing targeted prevention of stress-induced disorders in vulnerable populations.

Speaker

Molly Hyer Postdoctoral Fellow, Virginia Commonwealth University

Hippocampal cellular profiles associated with cognitive flexibility in captive raccoons

Hippocampal cellular profiles associated with cognitive flexibility in captive raccoons. J. Jacob1, J. Drake1, E. Ploppert1, S. Benson-Amram2, M. Kent1, S. Daniels2, R. Fanelli2, A. Gilbert4, S. Johnson4, A. Lai1, A. Miller3, N. Natale1, S. Herculano-Houzel3, K. Lambert1. 1University of Richmond, Richmond, VA, USA, 2University of Wyoming, Laramie, WY, USA, 3Vanderbilt University, Nashville, TN, USA, 4USDA/APHIS, Fort Collins, CO, USA. While the predominant mammalian model used in biomedical research is comprised of rodents such as the laboratory rat (Rattus norvegicus), the translational potential has proven especially limited when studying diseases of the brain. Raccoons (Procyon lotor) offer a unique approach to studying the mammalian brain, as these animals are capable of performing complex tasks and have a well-established history of flexibility and adaptation. Here, we acquired brain tissue from captive raccoons assessed for individual problem-solving capabilities utilizing a multi-access puzzle box, designed with three different solution options to test for behavioral flexibility. Raccoons that solved all three puzzles (n=7) were compared with those that solved none of the puzzles (n=6) and animals that partially solved the puzzle (n=8). Following testing, select regions from one hemisphere of each brain were processed for isotropic fractionation, a method that quantifies overall cell density for targeted areas. The hippocampus (HC) and somatosensory cortex (SSCX) were quantified first, given their potential role in mediating problem-solving abilities. No differences were found in the SSCX, yet total HC cell counts in problem-solving raccoons averaged 30% higher, differing from both intermediates (p=0.03) and non-solvers (p=0.02). Preliminary studies investigating neuron:glia ratios in the HC of the three groups indicate no differences in neuron percentages, suggesting the higher hippocampal cell numbers in the problem-solvers is driven by higher glial counts. Brain sections stained with cresyl violet indicated evidence of von Economo neurons in the insular cortex and 'œvon Economo-like' neurons in the HC. No statistically significant differences were detected, though von-Economo-like neurons are more prevalent in the problem-solving raccoons (xl„=4.6 vs. 2.3, p=0.13). Additional immunohistochemistry studies investigating expression profiles of neurotrophic factors such as BDNF and NMDA2A/2B ratios in these raccoon brain slices are currently underway.

Speaker

Jacy Jacob Trawick Postdoctoral Scholar in Behavioral Neuroscience, University of Richmond

Maternal preconception nicotine and enrichment confer long-term consequences on offspring behavior in a sex-dependent manner

Maternal preconception nicotine and enrichment confer long-term consequences on offspring behavior in a sex-dependent manner

Serena Jenkins, Allonna Harker, Robbin Gibb
Canadian Center for Behavioral Neuroscience, University of Lethbridge, Alberta, Canada

Substantial evidence now demonstrates that parental exposure to drugs of abuse can influence the development of subsequent generations. However, relatively little research has examined how positive experiences can be inherited across generations, and if positive experience can mitigate the intergenerational effects of drug use. I will present that maternal preconception environmental enrichment and chronic nicotine exposure interact to confer long-term consequences on adult offspring behavior. Environmental enrichment involved housing animals in an environment that was both socially and contextually enriched relative to standard laboratory-style housing. Nicotine was chosen as the drug of abuse due to its prevalence in populations across levels of socioeconomic status and previous findings regarding its transmission from one generation to the next. Female Long Evans rats were housed in either standard or enriched conditions beginning in adolescence and continuing until immediately prior to conception. Half of the females per housing condition were exposed to moderate quantities of nicotine in their drinking water (15mg/L) for seven weeks prior to conception, which is the length of the spermatogenic cycle in male Long Evans rats and was chosen to complement the paternal exposure studies. The day following cessation of both the nicotine and housing treatments, females were paired with a naÃ¯ve male Long Evans rat. Offspring behavioral development was assessed in adulthood, including measures of emotional regulation, motor control, and learning and memory. Major findings indicate that both maternal preconception nicotine and enrichment impact adult offspring behavior, and that the two experiences often interact. Furthermore, the effects were largely sex-dependent with male and female offspring being differently affected on all measures.

Funding provided by NSERC grant to RG and NSERC-PGS-D scholarship to SJ.

Speaker

Serena Jenkins PhD Candidate, University of Lethbridge

CAMKII-DEPENDENT PHOSPHORYLATION OF HOMER2 MAINTAINS BINGE-DRINKING

CAMKII-dependent phosphorylation of Homer2 maintains binge-drinking. C.L. Jimenez Chavez,1 E. Van Doren,1 N.A. Williams,1 K.M. Huber,2 K.K. Szumlinski 11 Department of Psychological and Brain Sciences, University of California, Santa Barbara, Santa Barbara, CA2 Department of Neuroscience, University of Texas Southwestern Medical Center, Dallas, TXHomer2 is a glutamate receptor-related post-synaptic scaffolding protein that is up-regulated throughout the extended amygdala, affecting both alcohol intake and intoxication. Homer2 is phosphorylated on S117/S216 by calcium-calmodulin kinase II alpha (CaMKII) and this phosphorylation causes a rapid dissociation of mGluR5-Homer2 binding of potential relevance to alcoholism-related behaviors. Here, mice with alanine point mutations at S117/216 were generated and back-crossed to a C57BL/6J background. Subsets of mice were subjected to a behavioral test battery to examine for the effects of the phospho-mutation upon measures of negative affect, spatial learning and memory, sensorimotor gating, and both basal and alcohol-induced changes in locomotor activity and motor coordination. Another subset of mice were assayed for alcohol, sucrose and quinine intake under limited-access procedures and for alcohol intake under continuous-access procedures. When compared to age- and sex-matched wild-type (WT) mice, Homer2 phospho-mutants exhibited less anxiety-like behavior in the elevated plus maze and light-dark shuttle-box test, but did not differ from WT with respect to behavior in any of the other assays in the behavioral test battery or locomotor response to alcohol. However, both male and female phospho-mutants binge-drank less alcohol under modified Drinking-in-the-Dark procedures‴ a phenotype that extended to sucrose solutions, but not to quinine solutions. Notably, male and female mutant mice tended to consume more and less alcohol initially under continuous-access procedures, with initial alcohol intake inversely related to their acute sensitivity to 2 g/kg alcohol on the rotarod. However, this subject factor interaction in initial alcohol intake disappeared with subsequent experience drinking under continuous-access procedures. These findings provide new evidence that CaMKII alpha-dependent phosphorylation of Homer2 plays a relatively selective role in initiating binge-drinking of both alcohol- and sucrose-containing solutions.Funding provided by NIH/NIAAA grant AA024044 to KKS, NSF Fellowship to C.L.J.C.

Speaker

C Leonardo Jimenez Chavez Graduate Research Fellow, University of California, Santa Barbara

CacyBP/SIP and its targets in the rat spinal cord in norm and after transection.

CacyBP / SIP i jego cele w rdzeniu kręgowym szczura w normie i po przecięciu. Jurewicz Ewelina, Miazga Krzysztof, Fabczak Hanna, Sławińska Urszula, Filipek AnnaNencki Instytut Biologii Doświadczalnej PAN, ul. Pasteura 3, 02-093 Warszawa, Polska CacyBP / SIP to wielofunkcyjne białko, które posiada również aktywność fosfatazy. Celem tych badań była analiza lokalizacji i poziomu CacyBP / SIP oraz jego celów / substratów, fosforylowanego ERK1 / 2 (p-ERK1 / 2) i fosforylowanej kinazy białkowej aktywowanej mitogenem p38 (p-p38) w nienaruszony i przecięty rdzeń kręgowy. Za pomocą analizy Western blot / analizy densytometrycznej stwierdziliśmy, że w badanych fragmentach rdzenia kręgowego wyciętych 3 dni po przecięciu poziom badanych białek nie zmienił się istotnie, chociaż obserwowano tendencję spadkową w przypadku CacyBP / SIP oraz wzrostową w przypadku p-ERK1 / 2 i p-p38 w porównaniu z tkanką nienaruszoną. Bardziej wyraźne zmiany, tj. Spadek poziomu CacyBP / SIP oraz wzrost poziomu p-ERK1 / 2 i p-p38, zaobserwowano we fragmentach rdzenia kręgowego wyciętych 1 i 3 miesiące po przecięciu. Wyniki te zostały potwierdzone przez barwienie immunofluorescencyjne skrawków rdzenia kręgowego. Co więcej, podwójne barwienie immunofluorescencyjne przeprowadzone na tych skrawkach wykazało, że marker neuronalny, NeuN i marker oligodendrocytów, Olig2, jest współlokalizowany z CacyBP / SIP, p-ERK1 / 2 lub p-p38. A zatem,

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Speaker

Ewelina Jurewicz PhD, Nencki Institute of Experimental Biology, Polish Academy of Sciences

Involvement of a novel thalamo-preoptic neuronal pathway in social interaction using chemogenetics in rat

Involvement of a novel thalamo-preoptic neuronal pathway in social interaction using chemogenetics in rat. Keller, Dávid 1; Láng, Tamás 1; Cservenák, Melinda 2; Fazekas, Emese A. 2; Dobolyi, Arpád 1,2. 1 Laboratory of Neuromorphology, Department of Anatomy, Histology and Embryology, Semmelweis University, Budapest, Hungary, 2 MTA-ELTE Laboratory of Molecular and Systems Neurobiology, Department of Physiology and Neurobiology, Eötvös Loránd University and the Hungarian Academy of Sciences, Budapest, Hungary. We previously identified the posterior intralaminar thalamic nucleus (PIL) as a relay station of socially relevant sensory information activating oxytocin-secreting neurons upon social encounter. Here, we addressed to functionally characterize PIL neurons projecting to the preoptic area of the hypothalamus during stress-free social interaction in rats. We determined the effect of selective chemogenetic stimulation of the preoptic area-projecting PIL neurons on the social interactions between familiar adult female rats using the DREADD technique. A retrogradely spreading adeno-associated virus (AAV) encoding Cre-recombinase was injected into the preoptic area, and labeled the PIL. Another AAV, which expressed Cre-dependent DREADD was injected into the PIL. Chemogenetic stimulation of the preoptic area-projecting PIL neurons increased the duration of direct social interactions between the animals. Projections from the PIL were analyzed using the spead of the Cre-dependent virus and also by traditional anterograde tract-tracing. Both techniques identified similar targets, such as the lateral septal nucleus, medial amygdala, paraventricular and dorsomedial hypothalamic nuclei and the infralimbic cortex. To test the functionality of these projections, the brain activation pattern was examined upon direct social interaction, and in response to chemogenetic activation of the PIL. Both approaches resulted in the activation of the previously anatomically identified target areas. The activation of these target areas was lower with the exlusion of direct physical contact during social interaction. The results suggest that the preoptic area projecting PIL neurons may convey socially relevant information to several other brain regions, which may participate in the control of social behaviors. Support: New National Excellence Program of the Ministry of Human Capacities, Excellence Program of the Semmelweis University, NKFIH-4300-1/2017-NKP_17 and OTKA

K116538.

Speaker

Dávid Keller PhD Student, Semmelweis University, Budapest

Quality or quantity? Comparing ad-libitum and restricted access to a western-style cafeteria diet on behaviour, metabolism and the gut microbiome in rats

Quality or quantity? Comparing ad-libitum and restricted access to a western-style cafeteria diet on behaviour, metabolism and the gut microbiome in ratsMichael D. Kendig, Ching Ho, Margaret J. MorrisDepartment of Pharmacology, School of Medical Sciences, UNSW Sydney, NSW AustraliaPoor diets are leading contributors to global disease burden by increasing the risk of several chronic diseases. Overconsumption of high-fat, high-sugar diets can have adverse effects on metabolism, cognition and the gut microbiome, and restricting energy intake can ameliorate these deficits. However, people may restrict energy intake without necessarily improving their diet quality, and the effects of eating a calorie-restricted (balanced) amount of an unhealthy diet are not well understood. Here we compared effects of unlimited or restricted access to a palatable western-style '˜cafeteria' diet (CAF) high in sugar and saturated fat in adult male Sprague-Dawley rats (n=12/group). Four experimental groups received ad libitum or restricted access to chow (CHOW-U and CHOW-R) or CAF diets (CAF-U and CAF-R) for 6 weeks. Energy intake of restricted groups was maintained at that of the CHOW-U group over the previous 24-h; this was provided in two daily rations given early in the dark phase approximately 3 h apart. The CAF-R group received the same foods as the CAF-U group but in smaller portions. As expected, the CAF-U group exhibited the greatest energy intake and weight gain, with doubled fat mass at endpoint relative to other groups. Despite isocaloric energy intake, retroperitoneal fat was elevated in CAF-R rats relative to those fed chow. Both continuous and restricted CAF access elevated fasting blood glucose and plasma triglyceride concentrations relative to chow, but plasma IL-6 was selectively increased in the CAF-R group. No effects on anxiety-like behaviour (week 4) or recognition memory (week 6) were observed, though restricted groups were more active. Global microbiome composition differed significantly between CAF and chow-fed rats but was not modulated by restriction. In summary, exposure to an unhealthy CAF diet produced adverse metabolic effects even when access was isocaloric to a control group and without effect on body weight gain.Acknowledgments: this work was supported by an NHMRC project grant to MJM.

Speaker

Mike Kendig Postdoctoral Research Fellow, UNSW Sydney

Diet-induced obesity alters sweet taste preference and brain reward circuitry in rats

Diet-induced obesity alters sweet taste preference and brain reward circuitry in rats Justine Fam1, Kelly J. Clemens1, R. Fred Westbrook1, Margaret J. Morris2, & Michael D. Kendig2*1. School of Psychology and 2. School of Medical Sciences, UNSW Sydney, NSW Australia.*presenting authorObesity is a global public health problem that is associated with metabolic dysfunction, cognitive impairment and altered brain reward circuitry. The specific pattern of altered reward processing observed in obesity consists of hyposensitive reward circuitry in the striatum (decreased basal levels of dopamine and its receptors; blunted activation in response to palatable food) coupled with a hypersensitive response to food-predictive cues. These changes may perpetuate overeating and hinder weight loss attempts in modern environments saturated with cues for highly palatable foods and beverages. It is thus critical to understand how obesity-induced neural changes in reward circuitry alter preference for natural rewards like sugar. We used a rat model to assess the effects of diet-induced obesity on sweet taste preference and expression of phosphorylated extracellular signal regulated kinase (pERK, an index of neuronal activity) in brain regions involved in taste perception (insular cortex) and reward processing (nucleus accumbens shell). Adult male Sprague-Dawley rats were fed standard chow (Con; n=16) or a palatable western-style cafeteria diet (Caf;

n=16) for 12 weeks. Sweet taste preference was assessed in a series of 15-min choice preference tests between 2%, 8% and 32% sucrose solutions (w/v) held before and after the diet intervention under water-restricted and sated conditions. Caf diet exposure trebled energy intake and doubled body weight gain (% gain from baseline Â± SEM: Caf = 76.1 Â± 4.5 vs. Con = 35.0 Â± 1.7). In post-diet tests held under water restriction, group Con consistently preferred higher concentrations of sucrose (i.e., 32% > 8% > 2%). By contrast, group Caf were indifferent to the two lower concentrations (8% vs. 2% sucrose) and increased preference for 32% vs. 2%. The Caf group made fewer licks for all concentrations, regardless of motivational state, suggestive of motivational deficits. Rats were transcardially perfused immediately after a final test involving exposure to a novel concentration of sucrose solution (20%). Consistent with the behavioural data, immunofluorescent staining revealed significantly reduced pERK expression in the nucleus accumbens shell and insular cortex in the Caf group. The implications for reward processing in obesity and the utility of lick cluster size measures in interpreting these changes will be discussed.Funding: work supported by a UNSW Sydney School of Medical Sciences Accelerator grant to MDK.

Speaker

Mike Kendig Postdoctoral Research Fellow, UNSW Sydney

Cannabinoids for the treatment of bipolar mania?

Cannabinoids for the treatment of bipolar mania?Johnny A. Kenton 1, Juliana dos Reis Bastos 2, Mark A. Geyer 1,3, Jared W. Young 1,3.1 Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA 92093-0804, USA. 2 Neuropsychopharmacology, Federal University of Minas Gerais, Brazil. 3 Research Service, VA San Diego Healthcare System, San Diego, CA, USA.Individuals with bipolar disorder (BD) have high lifetime prevalence rates (~70%) of cannabis use and are 6.8 times more likely to report lifetime cannabis use compared to healthy controls. Prevalence rates of cannabis use disorder are 7.2% in BD compared to 1.2% in general population. Causal mechanisms underlying the relationship between cannabis use and BD remain unclear. Î”9-tetrahydrocannabinol (THC), the active component of cannabis is an agonist at the cannabinoid type 1 (CB1) receptor. People with BD may initially use cannabis due to its reported calming properties. Determining whether cannabis-related treatments prove beneficial to BD-related mania are vitally needed. Reducing functioning of the dopamine transporter (DAT) using GBR12909 (GBR) recreates the hyperexploratory behavior of people with BD mania in the Behavioral Pattern Monitor (BPM). This model can be used to determine the impact of cannabinoid treatments on BD mania-relevant behaviors. C57BL/6J male and female mice were pre-treated with GBR (16 mg/kg) and treatment with THC (0.3, 1, or 3 mg/kg) or vehicle, then the CB1 antagonist AM251 20 min (0.3, 1, or 3 mg/kg) or vehicle in 2 studies (after a 2 week washout). GBR was administered 10 & treatments 20 min before testing in the mouse BPM for 45 min. Consistent with previous studies, GBR recreated the hyperexploratory behavior of BD mania in both studies as measured by increased activity ($Fs(3,119)>28$, $p<0.0001$), rearing ($Fs(3,119)>4$, $p<0.05$), and reduced spatial d ($Fs(3,119)>12$, $p<0.0001$). No interaction with sex was observed ($Fs<1$, ns). Both THC and the CB1 antagonist AM251 reduced activity ($Fs(3,119)>4$, $p<0.001$). THC did not affect rearing, but AM251 reduced rearing $F(3,119)=7.9$, $p<0.0001$). AM251 increased spatial d ($F(3,119)=4.8$, $p<0.005$), while THC tended to do so ($F(3,119)=2.7$, $p=0.0506$). None of these treatments directly interacted with GBR however ($Fs<2$, ns). GBR treatment again recreated BD mania-like hyperexploration, as measured by hyperactivity, hyperexploration, and reduced spatial d. Acute treatment with both the CB1 receptor antagonist AM251 and CB1 receptor partial agonist THC remediated some of these BD mania-like behaviors, although no specific interactions were observed. Thus, acute cannabinoid treatments can normalize abnormal behaviors in BD mania. The impact of long-term treatment, as seen in BD, remains to be examined.This work was supported by R01DA404535

Speaker

Johnny A. Kenton Postdoctoral Scholar, University of California San Diego

Safety Conditioning in Rats: The Role of the Infralimbic Cortex

Safety Conditioning in Rats: The Role of the Infralimbic Cortex Judith C. Kreutzmann 1,2 and Markus Fendt 1,31Institute for Pharmacology & Toxicology, Otto-von-Guericke University Magdeburg, Germany2Leibniz Institute for Neurobiology, Magdeburg, Germany3Center of Behavioral Brain Sciences, Otto-von-Guericke University Magdeburg, GermanyAccurate discrimination between danger and safety cues is essential for survival. With the neuroanatomical pathways of conditioned safety currently unknown, aim of the present study was to investigate whether the infralimbic cortex (IL) is a key brain region for conditioned safety. Based on evidence from fear extinction data, we hypothesize that the infralimbic cortex (IL) may be of importance for conditioned safety. In the present study, we therefore investigated the effects of neuropharmacological manipulations on the acquisition and recall of conditioned safety.Sprague Dawley rats were safety conditioned with a single-cue safety conditioning protocol utilizing the acoustic startle response paradigm. We first investigated the effects of temporary IL inactivation on the acquisition and recall of conditioned safety. Based on our finding, we equipped rats with osmotic mini-pumps attached to an infusion cannula aimed at the IL and investigated the effect of chronic IL disinhibition on conditioned safety. Our results demonstrate that explicit unpairings of aversive electric stimuli and safety cues (CS-) lead to a significant decrease of the startle magnitude upon presentation of the safety CS in the recall session. Temporary inactivation of the IL during conditioning did not affect the recall of conditioned safety, whereas IL inactivation during the recall session blocked the retention of conditioned safety. Temporary inactivation of the PL had no effect on safety memory. Chronic activation of the IL facilitated conditioned safety memory and reduced contextual fear.Concluding, our findings suggest that the IL is a critical brain region for the recall of safety memory. Because traumatized persons are often unable to make use of safety cues in order to inhibit fear, this finding is of clinical relevance and could potentially contribute to therapy optimization of anxiety-related psychiatric diseases.

Speaker

Judith Kreutzmann PhD Student, Otto-von-Guericke University

Early life seeding of a fast-acting amyloid-beta peptide accelerates plaque deposition and microgliosis in the hippocampus of AppNL-G-F mice with no impairment in spatial navigation.

Early life seeding of a fast-acting amyloid-beta peptide accelerates plaque deposition and microgliosis in the hippocampus of AppNL-G-F mice with no impairment in spatial navigation. Lacoursiere, Sean G 1, Mohajerani, Majid H 1, Westaway, David 2, Safar, Jiri G 3, Sutherland, Robert J 1. 1 University of Lethbridge, 2 University of Alberta, 3 Case Western Reserve University. A characteristic of Alzheimer's disease is the prion-like propagation of amyloid-beta (AB). It has been hypothesized AB plaque spread and aggregation contributes to impaired cognition. However, the pathological effects of AB in the hippocampus are still unclear. To determine the causal role of AB in the hippocampus, we seeded AppNL-G-F mice with a fast-acting AB homogenate to initiate AB pathology early in life. Mice were randomized into four groups based on genotype (homozygous positive or negative) and homogenate (fast-acting or control). The medial entorhinal cortices of mice were intracerebrally seeded at 2 months of age with 1 uL of seed/hemisphere. Mice were tested on a battery of memory tasks at 3, 4.5, and 6 months of age; tasks included the Morris water task, balance beam, novel object recognition, and context fear conditioning. By accelerating AB pathology early in life, we were able to test the effects of AB without age being a confounding factor. Throughout the life of the mice and across the behavioural tasks, surprisingly little cognitive impairment was found despite immunohistochemical staining showing dramatically increased AB plaque (82E1) and microgliosis (Iba1) in the homozygous positive mice seeded with the fast-acting homogenate at 3 months of age. We found no significant correlation between AB plaque pathology in the hippocampus and spatial navigation ability, but object memory may have been impaired. There are several interpretations of this data, opening up several important questions on the amyloid cascade hypothesis. If AB aggregation alone does not cause cognitive impairment, what is causing impairment in AB based mouse models? How resilient is the brain to AB pathology? Could AB aggregation be protective? Despite these open questions, our results imply that AB plaque alone is not directly a causal agent for memory impairment. Funding: Alberta Prion Research Institute, Alzheimer Society of Alberta and Northwest Territories, Alzheimer Society of Canada, Canadian Institute for Health Research, NSERC Collaborative Research and Training Experience Program

Speaker

Sean Lacoursiere University of Lethbridge

Exploring social avoidance in the Fragile X Mouse model of ASD using a social fear conditioning paradigm

Exploring social avoidance in the Fragile X Mouse model of ASD using a social fear conditioning paradigmMia L Langguth 1 and Michael T Bowen 1.1 Brain and Mind Centre, University of Sydney, Sydney, Australia.Fragile X Syndrome (FXS), a form of intellectual disability in humans, is the most prevalent monogenetic cause of Autism Spectrum Disorder (ASD). FXS is caused by a single gene mutation in the FMR1 gene that causes loss of function to the fragile X mental retardation protein (FMRP), which plays a key role in regulating the expression of a wide range of proteins important in healthy cognitive development. Like humans with the fmr1 loss of function mutation, Fmr1(-/-) mice have deficits in social interaction and motivation as well as locomotion, repetitive grooming and anxiety-like behaviours. Social anxiety and avoidance is the most prevalent social deficit in patients with Fragile X Syndrome, present in as many as 75% of males. Until recently, however, behavioural phenotyping of sociability has been limited in its ability to isolate aspects of social interaction from social fear. Using a novel murine social fear conditioning (SFC) task, we pair a mild foot shock with conspecific social interaction and examine fear extinction and recall profiles, so we can isolate social fear to better understand the underlying aetiology. We will present data exploring how age (juvenile vs adult), sex (male vs female) and genotype (wild type vs FMR1(-/-)) impact conditioned social avoidance behaviour. This is thus the first ever work to properly model the core social deficit in Fragile X Syndrome in the FMR1(-/-) mice. Having established our model, we plan to investigate potential pharmacological therapeutics and the neural correlates of the social fear response behaviour using fibre photometry to tie social avoidant behaviour to real-time brain activity. This work was supported by Australian National Health and Medical Research Council (1092046, 1166044) funding to Michael Bowen and the Anna Donald Gift Fund.

Speaker

Mia Langguth PhD Candidate, University of Sydney

Zebrafish provide an important translational model for identifying toxicants that pose risk to neurobehavioral development

Zebrafish provide an important translational model for identifying toxicants that pose risk to neurobehavioral developmentEdward D. Levin, Zade Holloway and Andrew HawkeyDuke University Medical Center, Durham, NC, USAZebrafish with its clear chorion and variety of reporter systems provide an excellent model for the investigation of the cellular and molecular mechanisms of development in general and neurodevelopment in particular. A wide range battery of behavioral tests from evaluations of sensorimotor and emotional response to cognitive function and social interaction have been developed for zebrafish. Over the past two decades we along with other labs in the field have found that zebrafish provide important information filling the gap between high through-put in vitro assays to classic mammalian studies of complex behavioral function in the study of neurobehavioral toxicology. The in vitro studies can test many compounds quickly but provide no information about impacts on behavioral function. Although rodent and primate studies can provide detailed behavioral information they are too slow and costly to vet the more than 80,000 environmental contaminants of concern. Zebrafish provide a low-cost model that provides important functional behavioral information. We have found that early developmental exposure of zebrafish to low doses of pesticides that do not cause dysmorphogenesis or increased lethality do cause persisting impairments in behavioral function. Particularly sensitive has been the novel tank diving test which like the elevated plus maze in rodents indexes the balance between anxiety-like and risk-taking behavior. We have found persisting impairments in normal novel tank diving behavior in zebrafish with short (0-5 days post-fertilization) exposure to the organophosphate pesticides

chlorpyrifos and diazinon and the neonicotinoid pesticide imidacloprid. The zebrafish model of neurobehavioral toxicity is being used to screen a variety of classes of environmental toxicants such as heavy metals, flame retardants and polycyclic aromatic hydrocarbons as well as drugs such as nicotine, ethanol and valproic acid to help determine developmental neurotoxic risk and understand mechanisms of neurobehavioral toxicity.This research was supported by the Duke University Superfund Research Center (ES010356).

Speaker

Edward Levin Professor of Psychiatry, Duke University Medical Center

In Vivo Studies of the Role of ERK1/2 Phosphatase MKP3 in Dopaminergic Neurons on Cocaine-Associated Dopamine Signaling, Gene Expression and Behavior

In Vivo Studies of the Role of ERK1/2 Phosphatase MKP3 in Dopaminergic Neurons on Cocaine-Associated Dopamine Signaling, Gene Expression and BehaviorStacia I. Lewandowski 1, David L. Bernstein, Ph.D., 2, Rodrigo A. EspaÃ±a, Ph.D.,3, Ole V. Mortensen, Ph.D., 4.1Pharmacology & Physiology, Drexel University College of Medicine, Philadelphia, PA, USA.2Neurobiology & Anatomy, Drexel University College of Medicine, Philadelphia, PA, USA.3Neurobiology & Anatomy, Drexel University College of Medicine, Philadelphia, PA, USA.4Pharmacology & Physiology, Drexel University College of Medicine, Philadelphia, PA, USA.Abundant evidence indicates that repeated exposure to cocaine results in cellular and molecular changes in the mesolimbic dopamine system, reorienting behavior towards drug seeking and drug use. Despite this knowledge, there are no FDA-approved pharmacotherapies for cocaine use disorder, suggesting that we need a more detailed understanding of the neurobiology that underlies cocaine addiction. Cocaine exerts its addictive effects by blocking the dopamine transporter (DAT), leading to excess dopamine (DA) in the synaptic cleft, resulting in the euphoric 'œhigh' that is often sought-after during addiction. The ERK1/2 Map Kinase signaling pathway has been implicated in the locomotor-stimulant effects of psychostimulants such as cocaine, as well as the sensitization effects induced by repeated cocaine administration. It is imperative to identify specific downstream targets of this pathway to reveal novel therapeutic targets for treating cocaine use disorders. In this study we describe the modulation of the ERK1/2 pathway in vivo by specifically expressing the ERK1/2 phosphatase MKP3 only in dopaminergic cells. We have generated adeno-associated viral (AAV) vectors with Cre recombinase (Cre)-dependent expression of MKP3 resulting in a decrease of the ERK1/2 signaling specifically in DA cells of the ventral tegmental area (VTA). This construct was injected into the VTA of Long Evans rats expressing Cre in tyrosine hydroxylase positive cells (TH-Cre rats). We have demonstrated that inhibiting ERK1/2 signaling in DA neurons of the VTA decreases cocaine-induced locomotor sensitization and attenuates the motivation to obtain cocaine during self-administration. Additionally, we have demonstrated via in vivo fast scan cyclic voltammetry (FSCV) that inhibition of ERK1/2 signaling in DA neurons influences the function of the dopamine transporter (DAT) in the nucleus accumbens (NAc) and ev vivo brain slice biotinylation has determined that MKP3 overexpressing rats have higher striatal DAT cell surface expression. We hypothesize that this increased DAT cell surface expression has a profound impact on behaviors associated with cocaine use. Also, studies utilizing Viral Translating Ribosomal Affinity Purification (vTRAP) and resulting RNA-Seq data demonstrate upregulation of dopaminergic genes, such as tyrosine hydroxylase and the dopamine transporter, which has been confirmed via biochemistry experiments. We believe these studies could have potential for identifying novel therapeutic targets for the treatment of cocaine use disorders.

Responding for a conditioned reinforcer does not predict risky decision making in rats

Responding for a conditioned reinforcer does not predict risky decision making in rats. Li, Andrew 1; Tremblay, Melanie 1; Winstanley; Catharine 1. 1 University of British Columbia. Drug-paired cues are believed to play an important role in maintaining the addicted state, and in triggering relapse. As well, salient stimuli are also also omnipresent in casinos, and may sustain or exacerbate gambling behaviours. Cues that are predictive of a reward increases the release of brain dopamine, and this dopamine efflux is maximal when the reward is probabilistic. Therefore, it has been suggested that both repeated choice of uncertain options, and repeated exposure to cues that predict reward with maximal uncertainty, may sensitize the dopamine system and thereby predispose subjects to the development of an addiction disorder. As such, the present study examined if there was a relationship between animals' tendency to

respond for a conditioned reinforcement (CRf) and risky decision making on the cued version of the Rat Gambling Task (cued rGT). Responding for CRf was tested either before (n = 16) or after (n = 16) acquisition of the cRGT. For, rats were trained to discriminate between two pavlovian stimuli (cue light). One light (CS+) was paired with sucrose delivery and the othe was (CS-) was paired with the absence of sucrose delivery. As well, they were trained to perform the rat gambling cast (cued rGT) in which salient cues accompany reward delivery. In this task, animals chose between four options associated with different magnitude and frequencies of rewards and punishing times-outs. Favouring the low-risk, low-reward task is the optimal strategy as this results in the greatest overall amount of sucrose pellets. The high-risk, high-reward option may seem tempting but it results in longer and more frequent time outs and therefore less reward overall. Contrary to our hypothesis, higher rates of responding for CRf prior to training on the cued rGT was associated with a better choice strategy, less motor impulsivity, and more trials completed on task. As well, cued rGT training did not increase rats' motivation to respond for CRf. Instead there was no evidence of any association between responding for CRf and risky choice when the CRf test occurs after cued rGT training. These results suggests that rat's performance of simple cue-driven behaviours do not readily inform our understanding of how cues influence more complex tests of cos-benefit decision making.

Speaker

Andrew Li https://andrewli.psych.ubc.ca, University of British Columbia

The effects of nicotinamide mononucleotide on chemotherapy-induced cognitive impairment

The effects of nicotinamide mononucleotide on chemotherapy-induced cognitive impairmentCatherine Li1, Emily Si2, Ian Johnston2, Timothy Chalmers1, Nicole Jones1, Caroline Rae3, David Sinclair4, Lindsay Wu1 1 School of Medical Sciences, UNSW Sydney, Australia 2 School of Psychology, The University of Sydney, Australia3 Neuroscience Research Australia, Australia4 Department of Genetics, Harvard University, USA The improvement in survival rates of cancer patients has rapidly increased due to the development of chemotherapeutic treatment regimes. With improved survival rates, there has-also been a rise in patients experiencing long-term side effects such as chemotherapy-induced cognitive impairments (CICI). CICI is the deterioration of cognitive function during and after chemotherapy, for which currently there are no available treatments. Chemotherapeutic agents such as doxorubicin (DOX) induce widespread DNA damage, including in healthy tissue such as the brain, leading to cognitive deficits that significantly impact the quality of life of cancer patients. The response to this DNA damage involves the activation of enzymes that consume nicotinamide adenine dinucleotide (NAD+), an essential metabolite required for a range of important processes such as DNA repair and glucose metabolism. We speculated that increased consumption of NAD+ during chemotherapy treatment might underlie chemotherapy-induced cognitive impairment (CICI), and to address this we tested the ability of the NAD+ precursor nicotinamide mononucleotide (NMN) to prevent CICI. We undertook a detailed proteomic and metabolomics analysis of the hippocampus from these animals and found signaling pathways that were dysregulated with doxorubicin treatment and possibly rescued with NMN. These data point to a new potential mechanism for CICI, as well as a therapeutic strategy that could intervene in this process.

Speaker

Catherine Li PhD student, UNSW

The basolateral amygdala mediates the retrieval of both recent and remote cued fear memory in rats

The basolateral amygdala mediates the retrieval of both recent and remote cued fear memory in ratsJianfeng Liu 1, Stephen Maren 1*1 Department of Psychological and Brain Sciences and Institute for Neuroscience, Texas A&M University, College Station, Texas 77843-3474*Corresponding author: maren@tame.eduAbstractAfter initial encoding in the brain, memory undergoes reorganization with the

passage of time. It has been demonstrated that different brain circuits underlie the retrieval of recent and remote fear memories in animal models. Despite extensive evidence about the critical role of the basolateral amygdala (BLA) in fear memory, there are controversial results on the involvement of the BLA in the retrieval of remote fear memory. In this study, we show that optogenetic inhibition of the BLA reduces retrieval of both recent and remote fear memory in male rats. To inhibit neuronal activity in the BLA, we expressed the red-shift microbial rhodopsin Jaws (AAV5-CaMKII-Jaws-EGFP) or a control EGFP. Rats were then conditioned in a within-subject procedure in which one conditioned stimulus (CS1; 8 kHz tone) was paired with footshock 14 days (remote memory) prior to testing, and a second CS (CS2; 2 kHz tone) was conditioned 1 day in a distinct context prior to testing. Retrieval testing to each CS was conducted in four counterbalanced tests (i.e., there were two tests for each CS, one with light on and the other with light off) and freezing behavior served as the index of conditional fear. We found that optogenetic inhibition of the BLA (red light, 635 nm, continuous illumination starting 10 sec before the first CS test trial) significantly attenuated freezing behavior to both the remotely and recently conditioned CS; rats expressing the control virus did not exhibit memory deficits. Consistent with previous lesion studies, the present study indicates that the BLA is essential for the retrieval of both recent and remote cued fear memory.Acknowledgements: This work was supported by the National Institutes of Health (R01MH065961 and R01MH117852 to S.M).

Speaker

Jianfeng Liu Postdoctoral fellow, Texas A&M University

Comparative Study of Emotional Sphere and the Ultrastructure of Central Amygdala in Adolescent, Adult and Senescent Rats

Comparative Study of Emotional Sphere and the Ultrastructure of Central Amygdala in Adolescent, Adult and Senescent RatsNino Lomidze1, Nino Pochkhidze1,2, Irina Sharikadze1, Nadezhda Japaridze2, Mzia G Zhvania1,21School of Natural Sciences and Medicine, Ilia State University, 0162 Tbilisi, Georgia2Department of Brain Ultrastructure and Nanoarchitecture, Ivane Beritashvili Center of Experimental Biomedicine, 0160 Tbilisi, GeorgiaAging is time-related decline of physiological functions, which has its effects on the molecules, cells, gross morphology at the level of different systems and alters behavioral and social processes. The brain is especially vulnerable to the aging. Although the relationship between behavior and brain structure may alter across the lifespan, the changes in these domains will ultimately be related. Using complex behavioral and electron microscopic approach, we clarify emotional sphere in adolescent, adult and senescent rats, as well as the ultrastructure/presynaptic architecture of central amygdala '" brain region, which plays one of the key roles in emotional behavior. Emotional sphere was studied using appropriate behavioral tests - in open field and cross maze. Behavioral analysis revealed no significant difference between adolescent and adult rats, while in senescent rats increased anxiety-like behavior was detected. Like behavioral tests, electron microscopic analysis did not show significant difference between adolescent and adult rats. However, in some neurons and glia cells of senescent rats, specific ultrastructure was noticed. This included lipopigment aggregates, as well as moderate changes in lysosomal hydrolytic activity, energetic system, protein import apparatus, and neuronal processes. In some cells ultrastructural features of compensatory processes were detected. Quantitative electron microscopic analysis has shown the effect of aging on the length of active zone, number and area of presynaptic profiles and number and area of presynaptic mitochondria. This effect, which was more prominent in senescent rats, indicate to alterations in neurotransmission and energy production needed for transmission. In general, the data show that normal aging, producing some changes in emotional sphere, does not affect significantly the fine structure of brain region, actively involved in emotional responses.Acknowledgments. This research is supported by Shota Rustaveli National Science Foundation:Grants # PHDF-18-1146

Speaker

Nino Lomidze PhD student, Ilia State University

Ultra-long-lasting naloxone

Ultra-long-lasting naloxone Caitlin A. Madison, Meenakshi Arora, MNV Ravi Kumar, and Shoshana EitanTexas A&M University, Department of Psychological and Brain SciencesOpioids, drugs derived from or designed to mimic opium, are powerful analgesics, but chronic use can lead to tolerance, dependence, or addiction which can result in dose escalation leading to accidental overdose. Due to opioid-induced respiratory depression (OIRD), overdose can be fatal. Naloxone, a mu-opioid receptor antagonist, can be used to reverse OIRD. However, the half-life of naloxone is shorter than that of many opioids. Thus, OIRD can return within 30-45 minutes post naloxone administration, a phenomenon known as renarcotization. Extended release naltrexone (VIVITROL) is marketed for intramuscular injection. However, VIVITROL was not approved by the FDA for the reversal of overdose, given the potential for severe withdrawal syndrome that might require hospitalization. In this study we designed and tested a novel oral naloxone formulated using polymer nanoparticles (NP-Naloxone). Naloxone has aversive properties, but otherwise it is believed to be safe and without easily detectable effects on its own in drug-naive mice. Therefore, in order to detect the duration of NP-naloxone action, we examined the duration for which NP-naloxone antagonized morphine-induced locomotion and antinociception. Antagonism of morphine-induced locomotion was detected within 1 min, and full onset of action was observed within approximately 5 min. Moreover, a single dose of 1 or 5 mg/kg NP-naloxone was highly effective at inhibiting the activating effects of repeated administration of 10 mg/kg morphine for at least up to 24 h. Importantly, in addition to its long action in antagonizing morphine's effects, NP-Naloxone precipitated significantly fewer withdrawal symptoms compared to injectable naloxone hydrochloride. At 1 mg/kg, NP-naloxone precipitated very minimal withdrawal behaviors. At the 5 mg/kg dose, NP-naloxone mitigate approximately 60% of the jumping withdrawal behaviors observed for injectable naloxone. Thus, this study demonstrates that orally administered naloxone based on polymer nanoparticles has high potential to be developed to circumvent OIRD and withdrawal symptoms.

Speaker

Caitlin Madison Graduate Research Assistant, PhD Student, Texas A&M University

The role of sociability levels in the response to opioids

The role of sociability levels in the response to opioids. Caitlin A Madison, Paul J Wellman, Shoshana Eitan. Texas A&M University, Department of Psychological and Brain Sciences.Individual social relationships and close social network has a great influence on the trajectory of developing opioid use disorder (OUD). Individuals interacting with others who use drugs, or even interacting with others who have a higher predisposition toward drug use due to their own socio-environment, have been shown to be more likely to exhibit drug use problems. Importantly, Individuals with different personality traits might have differential responses to the same social relationships and interactions. Thus, the present study tested the hypothesis that the responses to opioids is somewhat related to individual's sociability level. Mice were tested for their baseline sociability, anxiety levels, and pain sensitivities. Then, they were tested for their acute locomotor response to opioids. Subsequently, they were administered repeatedly with saline, hydrocodone, or morphine, and were examined for the expression of locomotor sensitization. This was followed by re-testing of anxiety levels and pain sensitivities. On the basis of their baseline sociability level, mice were divided into socially avoiding and socially exploring. Repeated administration of opioids had differential effects in socially avoiding and socially exploring mice. Socially exploring mice developed greater morphine locomotor sensitization than socially avoiding mice. This suggests that the trajectory to develop OUD in socially exploring individuals might be rooted in the interaction of opioids with the dopaminergic positive reward system. Socially avoiding mice, but not socially exploring mice, spent more time in the center zone of the open-field test and in the light zone of light/dark boxes, and developed heat hyperalgesia. This suggests that opioids might have greater interaction with the stress and pain systems in socially avoiding animals. Thus, the purpose for continuing opioid abuse and escalating to develop OUD might be rooted in enhancement of negative reinforcing processes. The underlying mechanisms for developing OUD might differ in individuals with various sociability levels.

Speaker

Caitlin Madison Graduate Research Assistant, PhD Student, Texas A&M University

Non-combat military service in older men impaired memory and cognitive flexibility in a virtual Morris water maze task.

Non-combat military service in older men impaired memory and cognitive flexibility in a virtual Morris water maze task. Magnusson, Kathy 1; Reynolds, Nadjalisse 1; Mollusky, Adina 1; Lee, Dylan 1; Zhong, Jimmy 2. 1 Dept Biomed Sci, Carlson Coll Vet Med. & Linus Pauling Inst., Oregon State Univ., Corvallis, OR; 2 School of Mechanical and Aerospace Engineering (MAE), Nanyang Technological University, Singapore. This study applied a virtual rendition of the Morris water maze (vMWM) task, which is commonly used for assessing spatial memory performance in rodents, to an examination of age-related differences among younger (18'"30 years; N=3-8) and older (60-86 year; N=9-18) male and female human participants and the impact of non-combat military service in older males (N=9) on spatial memory and cognitive flexibility. Participants performed the Logical Memory task (WMS IV), the NIH Toolbox Cognitive test battery, and cognitive tasks in vMWM task, including long-term memory, reversal, and working memory trials, followed by visible control trials, while seated at a computer desk. Older males performed significantly worse than young males on Logical Memory I (immediate recall; p=.023). Among older males, veterans performed significantly worse than civilians on the same task (p=.011). There were significant effects of age on all Toolbox measures (p range<.0001 to .047). Older males performed worse than young males (p<.0001) and older male veterans performed worse than older male civilians in the Crystallized Cognition Composite (p=.046). After controlling for age differences with corrected cumulative proximity in visible platform trials, older males showed significantly worse performance than young (p=.017) and veterans showed a trend for worse performance than civilians (p=.055) on probe trials for long-term memory. Older male veterans showed significantly poorer performance in reversal trials for cognitive flexibility than older male civilians (p=.028). This study provided novel findings showing that experiences with military support services may not yield positive effects lasting into old age. Research supported by a Large Program Development Award, Research Office, Oregon State University

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Speaker

Kathy Magnusson Professor & Principal Investigator, Oregon State Univ

Relationships between memory and flexibility performances in virtual Morris water maze and NIH Toolbox Cognitive Battery.

Relationships between memory and flexibility performances in virtual Morris water maze and NIH Toolbox Cognitive Battery. Reynolds, Nadjalisse 1; Mollusky, Adina 1; Lee, Dylan 1; Zhong, Jimmy 2; Magnusson, Kathy 1;. 1 Dept Biomed Sci, Carlson Coll Vet Med. & Linus Pauling Inst., Oregon State Univ., Corvallis, OR; 2 School of Mechanical and Aerospace Engineering (MAE), Nanyang Technological University, Singapore. This study examined the relationships between cognitive functions tested in virtual Morris water maze (vMWM) tasks and NIH Toolbox Cognitive Battery across aging. Younger (18'"31 years; N=3-8) and older (60-86 year; N=9-18) male and female human participants performed Logical Memory task (WMS IV), NIH Toolbox Cognitive Battery, and cognitive tasks in a vMWM, including long-term memory, reversal, working memory and visible control trials, while seated at a computer desk. In the long-term memory task, participants had no information that the platform would remain stationary during the first 12 hidden platform trials. They were then informed that the platform would remain stationary and performed an additional 12 trials. For reversal trials, the platform was moved to the opposite quadrant and they were informed that it had moved. For working memory trials, they were informed that the platform would move after every two trials. After locating a new position (naive trial), they searched again within 15 seconds (immediate trial). Hidden trials in the long-term memory task, after being informed about platform stability, correlated with flanker inhibitory control, list sorting, picture sequence memory, and fluid cognition composite scores (R=-.51-.65; p<.001). Average probe trials correlated with Logical Memory immediate recall (R=-.53;p=.0006). Reversal trials showed a relationship to Logical Memory recall after 50 minutes (R=-.518;p<.001) and averaged long-term memory hidden and probe trials (R=.53-.67; p<.0006). The immediate working memory trials

correlated with list sorting, flanker inhibitory control, pattern completion and fluid cognition composite scores (R=-.56-.74; p<.0003). This suggests that the vMWM tasks are relevant for human cognitive testing.

Speaker

Kathy Magnusson Professor & Principal Investigator, Oregon State Univ

Interaction between gestational immune activation and environmental enrichment on ER-alpha counts in the postpartum maternal rat hippocampus.

Interaction between gestational immune activation and environmental enrichment on ER-alpha counts in the postpartum maternal rat hippocampus. Nivethine Mahendran 1, Ruth Abebe 1, Matt Lukasic 1, Amanda C Kentner 2, Anne TM Konkle 1,3,4. 1Interdisciplinary School of Health Sciences, University of Ottawa ON. 2School of Arts & Sciences, Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts 3School of Psychology, University of Ottawa, Ottawa ON. 4University of Ottawa Brain and Mind Research Institute, Ottawa ON. The maternal brain experiences a high level of plasticity during pregnancy which is understood to be largely mediated by changes to the maternal immune, endocrine and nervous systems to prepare for offspring care. Given the prevalence of infections during pregnancy, the effect of gestational immune activation (GIA) on these systems and the maternal brain have not been fully characterized; in this work, GIA is used with respect to immune activation in the dams, instead of the maternal immune activation (MIA) terminology that is typically used for offspring exposure. In addition to this, the protective effects of environmental enrichment against biological stressors such as an infection have only been investigated within the context of MIA offspring. This study examines the effects of lipopolysaccharide (LPS) induced GIA and housing conditions on the postpartum maternal hippocampus. Sprague-Dawley rat dams (N=18) were randomly housed in one of three conditions: standard housing (ACC), social enrichment (SE), or environmental enrichment (EE). On gestational day 11 they were treated with either LPS or saline vehicle (VEH). Treatment was found to have an effect on ERalpha counts within the CA3 region of the hippocampus (F (1,12) = 334.8174; p= 0.021558) with LPS treated dams having lower mean ERalpha counts than VEH treated dams; 11.59 Â± 0.96 and 15.8 Â± 1.18, respectively. While there were no effects of housing alone, housing conditions do appear to mitigate the LPS-induced reductions in ERalpha counts in the CA3. These results demonstrate the potential for inflammatory processes during pregnancy to impact maternal brain plasticity, supporting the need for further research into the effects of GIA, especially in the era of SARS-CoV-2 outbreak.

Speaker

Nivethine Mahendran University of Ottawa

Sex Differences in the Aversive Effects of Methylone

Sex differences in the aversive effects of methylone. Hayley Manke 1, Katharine Nelson 1, Anna Vlachos 1, Jacob Bailey 1, Karina Maradiaga 1, Tania Weiss 1, Aikerim Imanalieva 1, Kenner Rice 2, Anthony Riley 1. 1 American University, Washington, DC, USA, 2 Drug Design and Synthesis Section, National Institute on Drug Abuse (NIDA), Bethesda, MD, USA. While methylone's rewarding effects have been well characterized, little is known about its aversive effects, a property that modulates the intake of abused drugs. In this context, this study investigated the aversive effects of methylone as assessed by taste avoidance conditioning, hyperthermia and hyperactivity). 35 male and 31 female Sprague-Dawley rats were given access to a saccharin solution followed by an intraperitoneal injection of methylone (0, 5.6, 10 or 18 mg/kg) every 4th day for a total of five trials. Following drug washout, subjects were randomly injected with various does of methylone and monitored for temperature by subcutaneous probes for 8 hours). Following a second washout, subjects were randomly injected with methylone or vehicle and motor activity (gross and stereotypes) was monitored for 1 hour. Given different baselines for male and female subjects, statistical analyses for each assessment were done separately for males and females using mixed model ANOVAs (p<

0.05). Methylone induced significant dose-dependent taste avoidance at all doses with females requiring an additional trial to acquire the aversion (all ps< 0.05). Males displayed dose- and time-dependent hyperthermia. Females initially displayed dose- and time-dependent hypothermia followed by hyperthermia (at lower doses than males). Males and females displayed time- and dose-dependent hyperactivity with males displaying faster onset and females displaying longer duration. Males and females displayed time- and dose-dependent stereotypies with no consistent differences.These findings parallel prior work with related bath salts, e.g., MDPV and Î±-PVP, although the specific mechanisms of action for these compounds differ. Given that drug intake appears to be a function of the balance of its rewarding and aversive effects, understanding both of these effects of methylone and the factors impacting them may provide insight into predicting its abuse potential. Financial Acknowledgement: Grant from the Mellon Foundation to ALR.

Speaker

Hayley Manke Doctoral Student, American University

Relationship between risk of mental health disorders and life habits

Relationship between risk of mental health disorders and life habits Yuhei Mashio and Hideo KawaguchiGraduate School of Life Sciences, Toyo University, Itakura, Gunma, JapanThe prevalence of mental health disorders has increased over time, especially in university students. Previously, we found it was possible to predict risk of mental health disorders by analyzing temporal information about handwriting using a digital pen. We then investigated the relationship between risk of mental health disorders and life habits to establish feasible coping strategies to be implemented at the individual level in a high-risk group. In total, 105 students aged 18'"22 years were recruited for a follow-up cohort study conducted over 2 years. Participants voluntarily completed the Uchida'"Kraepelin test using digital pens, as well as DIHAL.2, BDHQ, and PSQI questionnaires. Time intervals between first and second number strokes (4, 5, 7; mean time interval, t1) and between completion of a number and initiation of the next number (mean time interval, t2) were analyzed. Participants were classified into two groups according to the mean time interval ratio (t2/t1) observed each year. The high-risk group included participants with a t2/t1 â‰¥ 10 (n = 6), whereas the low-risk group included those with a t2/t1< 10 (n = 99) in year 2. The difference in questionnaire score between years 1 and 2 was calculated. Participant characteristics and questionnaire score differences were used to analyze differences between high- and low-risk groups. Using multiple logistic regression analysis, factors that were predictors of high-risk were evaluated. Significant differences were observed in the exercise type, sleep efficiency, dietary fiber intake, and Japanese food guide score (p< 0.05). A difference was also observed in the stress evasive actions in life habits (p< 0.10). High-risk was associated with the difference in sleep efficiency and stress evasive actions (OR = 3.47 and 0.72, respectively; p< 0.05). These findings suggest that interventions, including implementation of improving sleep efficiency, may improve mental health. This work was supported by Grants-in-Aid for Scientific Research to HK (KAKENHI, No. 17K01826) and THE INOUE ENRYO Memorial Grant of Toyo University (Itakura, Japan) to YM.

Speaker

Yuhei Mashio Toyo University

Effects of repetitive optogenetic stimulation of vglut2a-expressing spinal neurons on spinally-produced locomotor activity

Effects of repetitive optogenetic stimulation of vglut2a-expressing spinal neurons on spinally-produced locomotor activity. Montgomery, Jacob E, Wahlstrom-Helgren, S, Masino, MA. University of Minnesota, Twin-Cities.Central pattern generators (CPGs) are responsible for controlling the rhythmic outputs of a variety of essential functions, including respiration and locomotion. Locomotor CPGs in the spinal cord can be

induced to generate rhythmic locomotor activity through application of N-methyl-D-aspartate (NMDA) and through electrical stimulation. More recently, the advent of optogenetic technologies has allowed researchers to more precisely activate genetically-specified neuronal cell populations to investigate their roles within locomotor networks. Activation of spinal glutamatergic neurons with Channelrhodopsin-2 (ChR2) is sufficient to drive stereotyped locomotor activity in spinally-transected (spinalized) mice and larval zebrafish. Sustained ChR2-induced activation of spinal locomotor networks leads to a gradual decrease in locomotor activity throughout the stimulus and is likely a consequence of ChR2 desensitization. We found that the robustness of ChR2-induced locomotor activity was restored after an interval of rest in zebrafish larvae. However, it is not known how well, or if, ChR2-induced locomotor activity is maintained during repetitive blue light stimulation over long time periods. The objective of this study was to test the tolerance of this optogenetic activation paradigm to repetitive stimulation. Repetitive 10 s blue light stimuli were delivered to preparations at different intervals (1-15 min). Notably, locomotor activity persisted at all stimulus intervals, but was diminished after longer combined times of light exposure (i.e. more frequent stimulation). In comparison, corresponding timepoints of NMDA-induced swimming did not show a change in peripheral nerve burst number, but bursts became less well organized into discrete swimming episodes. Application of the neuromodulator dopamine had a depressive effect on ChR2-induced activity. This effect was reversible after washout, demonstrating that repetitive stimulation of glutamatergic neurons is an effective approach for activating locomotor circuitry to study the effects of neuromodulators on spinal CPGs.This work was supported by grants from the NIH (R01 NS094176) and Regenerative Medicine Minnesota.

Speaker

Mark Masino Associate Professor, University of Minnesota

Local D2- to D1-neuron transmodulation updates goal-directed learning in the striatum

Local D2- to D1-neuron transmodulation updates goal-directed learning in the striatumMatamales, Miriam 1; McGovern, Alice E. 2, Mi, Jia Dai 3; Mazzone, Stuart B. 2, Balleine, Bernard W. 1, Bertran-Gonzalez, Jesus 1.1 Decision Neuroscience Laboratory, School of Psychology, University of New South Wales, Sydney, NSW, Australia2 Department of Anatomy and Neuroscience, University of Melbourne, Melbourne, VIC, Australia.3 Department of Women and Children's Health, Faculty of Life Sciences and Medicine, King's College London, London SE1 7EH, United KingdomOne of the most intriguing characteristics of the striatum is the random spatial distribution and high degree of intermingling between its D1-(direct) and D2-(indirect) spiny projection neurons (SPNs). The resulting highly entropic mosaic extends through a homogeneous space and is mostly devoid of histological boundaries. The anatomical organisation of these two principal neuronal populations is actively promoted during development and has been highly conserved throughout evolution for over 500 million years, and yet its relationship to function is still not fully understood. In this study, by mapping a dopamine-dependent transcriptional activation marker in large ensembles of D1- or D2-SPNs in mice, we demonstrated an extensive and dynamic D2- to D1-SPN transmodulation across the striatum that is necessary for updating previous goal-directed learning. We found evidence that activated D2-SPNs access and modify developing behavioural programs encoded by regionally defined ensembles of transcriptionally active D1-SPNs. This process is slow because it depends on the molecular integration of additive neuromodulatory signals. However, with time, it creates the regional functional boundaries that are necessary to identify and shape specific learning in the striatum. Our work therefore suggests that the striatum takes full advantage of the '˜one-to-one' structure of the binary mosaic and provides unexpected insights into the peculiar histoanatomical organization of this disordered, borderless environment.Published in: Matamales M, McGovern AE, Mi JD, Mazzone SB, Balleine BW & Bertran-Gonzalez J (2020) Local D2- to D1-neuron transmodulation updates goal-directed learning in the striatum. Science. 367(6477):549'"555.This work was supported by the Australian Research Council (Grants DE160101275 to J.B.-G., DP19010251 to J.B.-G. and M.M. and DP150104878 to B.W.B.).

Speaker

Miriam Matamales University of New South Wales

Bidirectional pharmacological perturbations of the noradrenergic system differentially affect tactile detection

TitleBidirectional pharmacological perturbations of the noradrenergic system differentially affect tactile detection. AuthorsJim McBurney-Lin1,2,3, Yina Sun1,3, Lucas S. Tortorelli1, Quynh Anh Nguyen1,2, Sachiko Haga-Yamanaka1,2, and Hongdian Yang1,2. Author Affiliations1 Department of Molecular, Cell and Systems Biology, 2 Neuroscience Graduate Program, University of California, Riverside, CA 92521, USA, 3 These authors contributed equally to this work. AbstractThe brain neuromodulatory systems heavily influence behavioral and cognitive processes. Previous work has shown that norepinephrine (NE), a classic neuromodulator mainly derived from the locus coeruleus (LC), enhances neuronal responses to sensory stimuli. However, the role of the LC-NE system in modulating perceptual task performance is not well understood. In addition, systemic perturbation of NE signaling has often been proposed to specifically target the LC in functional studies, yet the assumption that localized (specific) and systemic (nonspecific) perturbations of LC-NE have the same behavioral impact remains largely untested. In this study, we trained mice to perform a head-fixed, quantitative tactile detection task, and administered an Î±2 adrenergic receptor agonist or antagonist to pharmacologically down- or up-regulate LC-NE activity, respectively. We addressed the outstanding question of how bidirectional perturbations of LC-NE activity affect tactile detection, and tested whether localized and systemic drug treatments exert the same behavioral effects. We found that both localized and systemic suppression of LC-NE impaired tactile detection by reducing motivation. Surprisingly, while locally activating LC-NE enabled mice to perform in a near-optimal regime, systemic activation impaired behavior by promoting impulsivity. Our results demonstrate that localized silencing and activation of LC-NE differentially affect tactile detection, and that localized and systemic NE activation induce distinct behavioral changes. Funding AcknowledgementThis work was supported by UCR startup (S.H.Y, H.Y.), UC Regents' Faculty Fellowship (H.Y.), Klingenstein- Simons Fellowship Awards in Neuroscience (H.Y.), and National Institute of Neurological Disorders and Stroke 1R01NS107355 and 1R01NS112200 (H.Y.).

Speaker

Jim McBurney-Lin PhD Candidate, University of California, Riverside

The subfornical organ is a neuroimmune hub regulating PTSD vulnerability

The subfornical organ is a neuroimmune hub regulating PTSD vulnerability. McMurray KMJ 1, Sah R 1,2. 1 University of Cincinnati, 2 VA, Cincinnati, OH. Post-traumatic stress disorder (PTSD) is a debilitating disorder associated with dysregulated fear processing. Evidence suggests PTSD patients are more sensitive to homeostatic stressors such as CO2 inhalation. CO2 inhalation triggers acidosis, evoking fear behaviors. A prior study in veterans found that pre-deployment CO2 sensitivity associated with trauma-induced PTSD symptoms suggesting CO2-sensitivity predicts vulnerability to develop PTSD following trauma. To understand the mechanisms and neurocircuitry contributing to this vulnerability, we developed a mouse model to examine the effect of CO2-inhalation on later PTSD relevant behaviors. We found that CO2 exposure increased shock-evoked fear extinction deficits one week later. Individual variability in CO2-responsivity correlated with fear extinction deficits, supporting a predictive role for CO2 sensitivity on later fear outcomes. In humans, PTSD associates with dysregulated neuroimmune interleukin-1 receptor (IL-1R) signaling. In mice, we reported that neuroimmune signaling within a blood brain barrier-devoid area, the subfornical organ (SFO), regulated acute fear responses to CO2. Here, we tested the hypothesis that inhibiting IL-1R signaling within SFO during CO2 inhalation would reduce CO2-evoked fear and later deficits in contextual fear extinction. IL-1R antagonist (IL-1ra) or vehicle was infused via SFO targeted cannulas 30m prior to 5% CO2 inhalation. One week later, mice underwent contextual fear conditioning. Sustained region-specific neural activity was quantified by IHC (FosB) in tissue collected 24h after final testing. We found that a single infusion of IL-1ra attenuated freezing (fear) during CO2-inhalation and reduced fear extinction deficits. IL-1ra also attenuated effects of CO2 inhalation on FosB expression within the infralimbic cortex. Given the well-established role of infralimbic cortex mediating extinction learning, we are currently using a chemogenetic strategy to inhibit SFO to infralimbic cortex projections during CO2 inhalation. Preliminary data suggest inhibiting this circuit reduces CO2-evoked fear. Collectively, our data provide the first evidence for neuroimmune mediators within the SFO regulating fear behavior and highlight SFO IL-1R as a novel

therapeutic target in PTSD. Supported by: VA Merit Grant & F32MH117913.

Speaker

Katherine McMurray Postdoctoral Fellow, University of Cincinnati

Sex-dependent associations between voluntary ethanol consumption and approach-avoidance conflict resolution

Sex-dependent associations between voluntary ethanol consumption and approach-avoidance conflict resolutionTanner A. McNamara, Rutsuko ItoDepartment of Psychology, University of Toronto at Scarborough, ON, CanadaApproach-avoidance conflict occurs upon encountering a stimulus carrying opposing positive and negative valences. Prior research demonstrated inherently rewarding and aversive properties of cocaine and ethanol, and cocaine exposure biasing male rats towards approach of cues predicting conflict, lending support to the idea that aberrant approach-avoidance conflict resolution may contribute to compulsive drug-seeking. However, little is known about the relationship between conflict resolution and voluntary ethanol consumption. This study explored the effects of voluntary ethanol drinking on conflict processing as well as the ability of conflict resolution and anxiety to predict drinking behaviour. Male and female Long-Evans rats self-administered ethanol in their homecages either before or after conflict behaviour was assessed in a Y-maze, and anxiety was assessed an elevated plus maze (EPM). Rats were trained in the Y-maze to associate three different visuo-tactile cues with no outcome (neutral), sucrose, and footshock. On the final test, rats had a choice between exploring an arm with neutral cues and an arm with sucrose and footshock cues paired to produce an approach-avoidance conflict. Females displayed a higher preference for and consumption of ethanol than male rats. Male rats showed a greater preference than female rats for the cues predicting conflict. Ethanol-exposed males compared to naÃ¯ve males, however, spent more time in the central hub and less time in both the arms despite a similar number of entries, indicating slowed decision making. In females only, a median split of cued-conflict preference scores revealed that the most conflict-averse group of rats displayed the highest preference for ethanol. In both sexes, ethanol history had no effect on cued-conflict preference and anxiety levels in EPM were unrelated to drinking behaviour. Our results highlight sex differences in both drinking and conflict resolution, and further suggest that cued-conflict preference should be examined as a potential predictor of drinking behaviour. Ethanol use may also affect the timing of decision-making in the face of conflict, even if decision-making itself remains unchanged. This work was funded by Canada Institutes of Health Research.

Speaker

Tanner McNamara PhD Student, University of Toronto at Scarborough

Endocannabinoid regulation of stress-induced escalation of cocaine intake in rats

Endocannabinoid regulation of stress-induced escalation of cocaine intake in rats. Jayme McReynolds1,2, Jacob Mathy1, Colten Wolf1, Dylan Starck1, Cecilia Hillard3, John Mantsch1. 1Marquette University, 2University of Cincinnati, 3Medical College of Wisconsin. Stress is an important contributing factor to addiction and is problematic as stress is unavoidable in daily life. Addiction can be characterized by a loss of control over drug intake that is modeled by escalating patterns of drug self-administration (SA). We have shown that a stressor, footshock, administered daily at the time of SA induces an escalation of cocaine intake. This is likely due to long-lasting neuroplastic changes that involve neurobiological mediators connecting stress and reward, such as endocannabinoids (eCB). These changes likely occur in regions implicated in both stress and reward, such as the nucleus accumbens (NAc) shell and ventral tegmental area (VTA). We hypothesize that repeated stress at the time of SA induces a persistent increase in eCB signaling in the NAc shell and VTA leading to escalation of cocaine use and increased susceptibility to reinstatement. Male rats were trained to SA cocaine in 4 X 30 min SA sessions separated by 5-min drug-free

periods. Some rats received shock in the SA chamber during the 5 min drug-free daily for 14 days. Systemic, intra-NAc, or intra-VTA administraion of the CB1R antagonist AM251 attenuated cocaine intake in stress-escalated rats. Cocaine SA with or without stress at the time of SA increases CB1R binding in the VTA while neither SA condition changes CB1R binding in the NAc. Other rats were tested for reinstatement of drug-seeking behavior to a priming injection of cocaine, footshock stress, or yohimbine. A history of shock during SA resulted in increased reinstatement to all three stimuli. Furthermore, as with SA, AM251 attenuated cocaine-primed reinstatement only in stress-escalated rats. We have begun to examine sex differences and our preliminary data indicate that female rats are more susceptible to stress-induced escalation of cocaine intake as they escalate more and faster. These data suggest that stress-induced neuroplastic changes occur, likely in the eCB system, in regions of the brain that influence expression of escalated cocaine intake and augmented cocaine-primed reinstatement and these changes may be glucocorticoid-dependent. Funded by NIDA Grant DA038663 to John Mantsch and CH & NIDA Grant K01DA045295 to Jayme McReynolds

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Speaker

Jayme McReynolds University Of Cincincinnati

Investigating tau pathology in a mouse model of Huntington's disease

Investigating tau pathology in a mouse model of Huntington’s disease.Mees, Isaline1; Tran, Harvey1; Li, Shanshan1; Roberts, Blaine1; Hannan, Anthony J.1; Renoir, Thibault11. Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne Brain Centre, Parkville, VIC 3010, Australia.Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expansion of a trinucleotide CAG repeat in the huntingtin (HTT) gene. Despite the discovery of the gene mutation in 1993, there are still no disease-modifying treatments available. Understanding the molecular and cellular mechanisms involved in HD is therefore crucial for the development of novel treatments. Tau is a soluble microtubule-associated protein featuring numerous phosphorylation sites. Similar to other degenerative disorders, recent pre-clinical and post-mortem clinical studies have shown the presence of hyperphosphorylated tau as well as tau aggregation in transgenic mouse models and HD brains. However, the implication of tau in HD pathology mechanisms remains unclear. To this end, we investigated changes occurring in tau expression and phosphorylation in the R6/1 mouse model of HD at a pre-symptomatic timepoint with western blots and a more global phosphoproteomics approach. We found the presence of tau hyperphosphorylation in the hippocampus, striatum and cortex, which are brain regions affected in HD. Interestingly, an immunohistological study showed the absence of aggregates made of hyperphosphorylated tau (AT8) in the same brain regions, at the late stage of the disease. Further ongoing experiments involve genetic interventions to discern the mechanisms underlying potential tau toxicity in HD. In conclusion, these results suggest that tau could be a potential target to delay onset, modify or treat HD symptomatology.This work was supported by a National Health and Medical Research (NHMRC) Project Grant. TR is a NHMRC Boosting Dementia Research Leadership Fellow. AJH is a NHMRC Principal Research Fellow. The Florey Institute of Neuroscience and Mental Health acknowledges the support from the Victorian Government’s Operational Infrastructure Support Grant

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Speaker

Isaline Mees PhD candidate, Florey Institute

Effects of early life adversity on eating behavior are moderated by genes co-expressed with Leptin Receptor

Effects of early life adversity on eating behavior are moderated by genes co-expressed with Leptin Receptor Lima, RMS 1; Barth, B2; Arcego, DM2; de MendonÃ§a Filho, EJ2; Patel, S2; Wang, Z2; Pokhvisneva, I2; Meaney, MJ2; Dalmaz, C1; Silveira, PP 2.1Universidade Federal do Rio Grande do Sul , Brazil2 McGill

University, CanadaLeptin is a hormone involved in the regulation of food intake, body weight and emotional behavior. The hypothalamus is an important region for regulating homeostatic responses. However, eating behavior is also modulated by systems involved in mood regulation and executive function, such as the prefrontal cortex. Exposure to early adversity is associated with changes in eating behavior and body weight regulation, but the mechanisms are still unknown. We propose to study interactions between early life adversity exposure and eating behavior associated with the leptin receptor gene network (LepR). For this, we constructed expression-based polygenic risk scores (ePRS) that reflect the function of prefrontal cortex or hypothalamus LepR gene networks, and analyzed their interactions with postnatal adversity exposure on eating behavior of healthy children in different samples. We used data from the Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) as our main cohort, and The Growing Up in Singapore Towards Healthy Outcomes (GUSTO) cohort based in Singapore was used as a replication cohort. The Child Eating Behaviour Questionnaire (CEBQ) was used to evaluate the relationship between children behaviour and food. The parents of 143 children (MAVAN) and 467 (GUSTO) were asked to answer questions about their child's behaviour. We observed in MAVAN a significant interaction between adversity and prefrontal-based LepR-ePRS on food enjoyment score at 48 months (Î²=61.58, p=0.015) and 72 months (Î²= 97.78, p=0.001), and on satiety score at 48 months (Î²=-43.63, p=0.046), with a trend at 72 months (Î²=-41.15, p=0.093), suggesting that an decrease in the expression of this gene network makes the subjects more vulnerable to early adversity effects, decreasing food enjoyment as early adversity increases. No effects were found using the hypothalamus-based LepR-ePRS. In GUSTO, the results were replicated. Our data supports the hypothesis that exposure to postnatal adversity affects eating behavior, and the PFC LepR gene network is an moderator of these effects. Funding: JPB Research Network on Toxic Stress.

Speaker

Randriely Merscher S. de Lima PhD candidate, Universidade Federal do Rio Grande do Sul

Maternal high-sugar diet during pregnancy and lactation in rats affects NMDA receptor composition, scaffolding proteins and miRNA regulation in the offspringâ€™s brain structures.

Maternal high-sugar diet during pregnancy and lactation in rats affects NMDA receptor composition, scaffolding proteins and miRNA regulation in the offspring's brain structures. Jozef Mizera1, Grzegorz Kazek2, Lucyna Pomierny-Chamiolo1. 1Department of Toxicology, Faculty of Pharmacy, Jagiellonian University Medical College, Cracow, Poland. 2Department of Pharmacological Screening, Faculty of Pharmacy, Jagiellonian University Medical College, Poland. Aims: Maternal non-balanced diet is suspected of causing long-term effects in the developing offspring such us depression, anxiety, schizophrenia, autism spectrum disorder or learning deficits. In the pathogenesis of neuropsychiatric disorders, the glutamatergic system and NMDA receptors activity plays an important role and can be extensively involved in the creation and development of abnormalities in the offspring. The aim of this study was to investigate the effect of maternal high-sugar diet during pregnancy and lactation on the NMDA receptors composition, scaffolding proteins and miRNA regulation in brain structures related to the memory function. Methods: Female Wistar rats were divided into 2 groups and fed with standard or high-sugar diet. 21-day-old offspring were separated form mothers and fed with standard diet. In the hippocampus and medial prefrontal cortex of 28- and 70-day-old offspring, the protein expression of NMDA receptors subunits and scaffolding proteins was determined using the Western blot method as well as selected mRNA and miRNA level using qPCR. Results: Maternal high-sugar diet caused an up-regulation of the GluN2B subunit in 28-day-old female and male offspring's hippocampus with a simultaneous increase in SAP-102 expression and decrease in miRNA-223 and miRNA-219 levels. Also, in males GluN1 and GluN2A subunit expression was increased. In the medial prefrontal cortex, the opposite effects were observed. Interestingly, in 70-day-old animals most of the observed changes have been reversed. Conclusions: Obtained results indicate that maternal high-sugar diet affects NMDA receptors composition and regulation. This may result in behavioral, metabolic and psychological disturbances. Acknowledgments: This study was supported by the grant 2015/19/D/NZ7/00082 from the National Science Centre, Poland.

Speaker

Józef Mizera Jagiellonian University Medical College, Faculty of Pharmacy

Longitudinal assessment of biomarkers for depression-like susceptibility in male and female mice

Longitudinal assessment of biomarkers for depression-like susceptibility in male and female mice Alice Morgunova (1,2), Ashraf Mahmud (1,2), Cecilia Flores (2,3).1) Integrated Program in Neuroscience, McGill University2) Douglas Mental Health Institute 3) Psychiatry Department, McGill UniversityBackground: Major depressive disorder (MDD) impacts approximately 5% of the world population, and it often emerges in adolescence, when the prefrontal cortex (PFC) is undergoing major maturational changes. The first gene to orchestrate the structural maturation of the PFC in adolescence is the guidance cue receptor Dcc. Dcc expression is regulated by microRNA called miR-218. The goal of this study is to assess Dcc and miR-218 expression during critical period of adolescence and whether their levels can predict vulnerability to depression in male and female mice. Methods: The mouse model chronic non-discriminatory social defeat stress (CNSDS) was used to assess depressive-like behavioral traits in male and female mice after repeated stress exposure. Then, novelty suppressed feeding, open field test, novel object recognition, and tail suspension tests were carried out. In a separate batch of animals, blood will be collected in adolescence and after the CNSDS in adulthood. RNA extraction and quantitative Real-Time PCR will be used to measure expression levels of miR-218 and Dcc. Results: Male and female mice show significant differences between susceptible and resilient phenotypes. Interestingly, unlike males, susceptible to depression-like behaviors female mice showed greater latency to feed, longer time in the center of the field, time spent exploring novel object, and time spent immobile. Conclusions: This study will be the first of its kind to elucidate (i) sex dependent molecular mechanisms underlying vulnerability to depression-like behaviors, and (ii) whether miR-218/Dcc pathway in adolescence plays a potent role in determining vulnerability to depression-like phenotypes. Funding Acknowledgement: This work was funded by Canadian Institute for Health Research (C.F. MOP-74709), the National Institute on Drug Abuse (C.F. R01DA037911), and the Natural Science and EngineeringResearch Council of Canada (C.F. 2982226).

Speaker

Alice Morgunova McGill University and Douglas Mental Health Institute

Investigating the Potential Antipsychotic effects of Cannabinoid Receptor Type 2 Modulation in a Rat Model of Schizophrenia

Investigating the Potential Antipsychotic effects of Cannabinoid Receptor Type 2 Modulation in a Rat Model of SchizophreniaShoaib Muhammad, Bryan Jenkins, Hayley Thorpe, Jude A. Frie, Jibran Y. KhokharDepartment of Biomedical Science, University of Guelph Introduction: The recent discovery of the role of the Cannabinoid Receptor Type 2 (CB2R) in regulating dopamine release in prefrontal cortex (PFC) neurons, suggest that modulation of this receptor could act as an effective treatment for schizophrenia. Additionally, the antipsychotic efficacy of muscarinic M4 allosteric modulators is also CB2R mediated, suggesting the need for investigating the antipsychotic potential of CB2R modulation. In this study we investigated the potential antipsychotic effects caused by CB2R modulation in the Neonatal Ventral Hippocampal Lesion (NVHL) rats using the CB2R antagonist HU-308 in Conditioned Avoidance Response (CAR) and Pre-pulse Inhibition (PPI) experiments. The NVHL rat model provides an effective model of schizophrenia that mimics many of the neurobiological and behavioural effects of this disorder. Methods: 16 Sprague Dawley rats (8NVHL, 8 Sham) underwent NVHL surgery at post-natal day (PND) 7. In adulthood, these animals were trained in for 13 days in CAR and habituated for 3 days for PPI before being administered vehicle and HU-308 treatments at a dose of 5 mg/kg on separate days. The animals subsequently underwent CAR and PPI experiments. CAR avoidance, escape and failure responses were recorded along with %PPI. Results: No significant differences were found in avoidance, escape, or failure responses between drug administration days. There was a main effect of drug treatment on %PPI for both NVHL and Sham rats, where HU-308 administration was associated with an increase in %PPI ($F(1,14) = 5.139$, $p=0.040$). Additionally, there was a main effect of surgery condition ($F(1,14) = 5.534$, $p=0.034$), where

NVHL animals were associated with a decrease in %PPI. HU-308 administration was unable to recover %PPI deficit in NVHL rats. Discussion: The results suggest that acute modulation of the CB2R does not have a significant antipsychotic effect as measured by the CAR and PPI experiments. However, this experiment did not evaluate the effects of CB2R modulation on the cognitive and negative symptoms of schizophrenia. Furthermore, the trial design made it impossible to separate the effects of HU-308 from the effect of habituation after continuous exposure to the PPI experiment. Over-training of the animals for CAR may have dampened the expression of a statistically significant difference between drug treatment days. This warrants future investigation with a more conventional trial design, shorter CAR training period, as well as the evaluation of sub-chronic, and long-term effects of CB2R modulation.

Speaker

Shoaib Muhammad Undergraduate Student, University of Guelph

Cognitive impairment of a maternal immune activation mouse model of schizophrenia assessed with the 5-choice serial reaction time (5-CSRT) task

Cognitive impairment of a maternal immune activation mouse model of schizophrenia assessed with the 5-choice serial reaction time (5-CSRT) taskEva Munarriz-Cuezva a,b, Blanca Perez-Palomar a,b, Javier J. Meana a,b,ca Department of Pharmacology, University of the Basque Country UPV/EHU, Leioa, Bizkaia, Spainb Centro de InvestigaciÃ³n BiomÃ©dica en Red de Salud Mental, CIBERSAM, Spainc Biocruces Bizkaia Health Research Institute, SpainExperimental and epidemiological evidence indicates that infections during pregnancy represent a risk factor to develop schizophrenia. Cognitive deficits are considered a key feature of schizophrenia symptoms. Animal models based on maternal immune activation with the viral mimetic Poly (I:C) during pregnancy have been developed. The 5-choice serial reaction time task (5-CSRTT) has been proposed as a translational behavioral test to evaluate procognitive drug candidates in schizophrenia.The aim of this study was to characterize the cognitive status of adult (60 PND) male offspring from Poly(I:C) immuno-activated and saline (control) pregnant mice. A touchscreen-based 5-CSRTT test was used to assess attention, cognitive flexibility and perseverant/impulsive behaviors. Animals were trained in a liquid-rewarding paradigm with a progressive reduction of the stimulus duration on the screen. Accuracy, omissions, perseverative and premature responses were quantified. Further, adaptations to a distracting noise and to randomized variations of the inter-trial delay time were tested. Along with the training, the Poly (I:C) offspring showed similar weight, preference for reward, accuracy and omission responses to controls. Drop-outs were similar between groups. When the complexity of the task increased by a distracting noise or randomized reductions of the delay time, increased omission rate and time response were observed, suggesting a slower processing speed.In conclusion, the Poly (I:C) mouse model of schizophrenia displayed attentional impairment with alterations that influence the normal cognitive flexibility. The model could be helpful for the study of pharmacological responses to candidate compounds for cognitive impairment associated with schizophrenia.

Speaker

Eva Munarriz-Cuezva Postdoctoral researcher, University of the Basque Country

SK609, a novel dopamine D3 receptor agonist and norepinephrine transporter blocker with pro-cognitive actions, does not induce psychostimulant-like increases in risky choice during probabilistic discounting

SK609, a novel dopamine D3 receptor agonist and norepinephrine transporter blocker with pro-cognitive actions, does not induce psychostimulant-like increases in risky choice during probabilistic discounting. Christopher Knapp1, Brooke Fallon1, Stan B. Floresco2, Sandhya Kortagere3, Barry D. Waterhouse1, Rachel L. Navarra11 Department of Cell Biology and Neuroscience, Rowan University School of Medicine, 2

Department of Psychology, University of British Columbia, 3 Department of Microbiology and Immunology, Drexel University College of MedicineCognitive and reward-related processes are modulated by catecholamine circuits, such as norepinephrine (NE) and dopamine (DA) input to the prefrontal cortex (PFC). Psychostimulants block reuptake and elevate extracellular concentrations of both NE and DA, and are common pharmacological strategies used to improve PFC-dependent behavioral dysfunction associated with neuropsychiatric disorders like attention deficit hyperactivity disorder (ADHD). However, this approach can be problematic given the side effect liability and abuse potential of psychostimulants. SK609 is a novel NE reuptake blocker that selectively activates DA D3 receptors without affinity for the DA transporter. SK609 has been shown to improve sustained attention similar to the ADHD-approved psychostimulant methylphenidate (MPH), but not produce MPH-like increases in spontaneous locomotor activity associated with DA transporter activity. These findings suggest SK609 may help ameliorate neurocognitive impairments without psychostimulant-like side effects. The probabilistic discounting task (PDT) is a well-established preclinical assay for risk/reward decision making that resembles risky gambling behavior in humans. Psychostimulant drugs such as amphetamine (AMPH) increase risky choice behavior on this task. While AMPH and MPH, as well as SK609 improve selected dimensions of PFC-mediated cognitive function, we now show the effects of SK609 can be dissociated from the psychostimulant drugs using the PDT. In well-trained male rats, AMPH and MPH increased risky choice at doses known to improve other forms of cognition, with this effect being driven by a reduction in sensitivity to non-rewarded risky choices (i.e.; lose-shift behavior). In contrast, SK609 did not affect overall risky choice, but tended to increase win-stay and lose-shift behavior, suggesting that this compound enhances the influence that recently rewarded and non-rewarded actions exert over subsequent choice. These data show SK609 has ability to produce favorable effects on behavioral outcomes in other domains of cognition mediated by the PFC, without psychostimulant-like side effect liability assessed with the PDT. These data also highlight the roles of NE transporter blockade and selective D3 activation in pro-cognitive action. The absence of DA transporter blockade and non-selective dopaminergic elevation are beneficial properties of SK609 that differentiates it from the traditional pro-cognitive psychostimulants.Funding sources: New Jersey Commission on Brain Injury Research CBIR20PIL004 (Navarra), CBIR19IRG025 and CBIR17PIL007 (Waterhouse)

Speaker

Rachel Navarra Assistant Professor, Rowan University

Ethanol pre-exposure differentially impacts the rewarding and aversive effects of a-pyrrolidinopentiophenone (a-PVP): Implications for drug use and abuse.

Ethanol pre-exposure differentially impacts the rewarding and aversive effects of a-pyrrolidinopentiophenone (a-PVP): Implications for drug use and abuse. Katharine H. Nelson1, Hayley N. Manke1, Jacob M. Bailey1, Anna Vlachos1, Karina J. Maradiaga1, Tania D. Weiss1, Shihui Huang1, Kenner C. Rice2 and Anthony L. Riley1.1Department of Neuroscience, American University, Washington, DC, USA; 2Drug Design and Synthesis Section, National Institute on Drug Abuse (NIDA), Bethesda, MD, USA. The aim of the present studies was to assess the impact of ethanol history on the rewarding (conditioned place preferences) and aversive (conditioned taste avoidance, hyperthermia and hyperactivity) effects of a-PVP. Male SD rats (n = 48) were intraperitoneally injected with ethanol (2 g/kg) or saline every 3rd day for 5 exposures. Following this, a combined taste avoidance/place preference procedure was used in which a saccharin solution was given followed by an injection of a-PVP (1.5, 3 or 5 mg/kg, IP) or vehicle (n = 6/group) followed by placement on one side of a CPP apparatus for 30 min. The next day, rats were given water, injected with saline and placed on the opposite side. This cycle was repeated 3x, followed by a final assessment of side preference. After a-PVP washout, rats were randomly injected with a-PVP then monitored for temperature by dermal probes for 8h. Following another washout, rats were injected with a-PVP or vehicle and motor activity was monitored for 1h. Mixed model ANOVAs were used for each assessment. Relative to vehicle pre-exposure, ethanol reduced a-PVP-induced aversions (ps â‰¤ 0.04). a-PVP induced place preferences (ps â‰¤ 0.042) with no effect of pre-exposure. a-PVP produced dose- and time-dependent increases in temperature (ps â‰¤ 0.038) with no effect of pre-exposure. a-PVP induced an increase in locomotion that was dose-, time- and pre-exposure-dependent (ps â‰¤ 0.027). Significant dose and time-dependent stereotypies were produced (ps< 0.000) with no effect of pre-exposure. Ethanol pre-exposure lessened several of the aversive effects of a-PVP, but had no impact on a-PVP's rewarding effect. Ethanol history may increase a-PVP's abuse potential. Funding: The Mellon Foundation (ALR), the College Arts and Sciences Graduate Research Award and The Center for Behavioral Neuroscience (KHN), and the NIH Intramural Research Programs of the National Institute on Drug Abuse (NIDA) (KCR), the National

Institute of Alcohol Abuse and Alcoholism (NIAAA) (KCR).

Speaker

Katharine Nelson Doctoral Candidate, American University

Cannabis and the brain: Effects of novel cannabis strains on behaviour and neuroanatomy in the Long-Evans rat.

Cannabis and the brain: Effects of novel cannabis strains on behaviour and neuroanatomy in the Long-Evans rat. Claire Niehaus 1, Allonna Harker 1, Olga Kovalchuk 1, Igor Kovalchuk 1, Robbin Gibb 1. 1. University of Lethbridge. Cannabis, a drug derived from the plant Cannabis sativa, is the most commonly used illicit drug worldwide. As the current social and legislative attitudes towards this drug begin to change, novel strains of cannabis are beginning to emerge, each with unique combinations of the major cannabinoids tetrahydrocannabinol (THC) and cannabidiol (CBD). The rapid development of new cannabis strains provides an unprecedented opportunity to conduct research into the effects of these different molecules, and combinations thereof, on the healthy state. This project uses a rodent model to examine the effects of novel high-CBD low-THC cannabis extracts on behavioural and neuroanatomical outcomes. We hypothesize that there will be an observable difference between the two strains in both behaviour and morphological measures of brain tissue. Four treatment groups of animals were orally administered one of two cannabis extracts in peanut butter at one of two dosages for 10 days: (1) extract 1 at 10mg/kg, (2) extract 1 at 40mg/kg, (3) extract 2 at 10mg/kg, (4) extract 2 at 40mg/kg. Control animals received no cannabis extract but followed an identical peanut butter dosing/testing paradigm. Behavioural testing was conducted during adolescence (pre-dosing) and adulthood (post-dosing) using a battery of well-established tests including activity box, elevated plus maze, Whishaw tray reaching, and Morris water task. These tasks were selected for their sensitivity to prefrontal and hippocampal changes; two brain areas susceptible to the effects of cannabis. Following adult behavioural testing, animals were euthanized and their brains extracted for anatomical analysis. Measures of prefrontal and hippocampal dendritic morphology and synaptic connectivity, as well as gross measures of cortical thickness and thalamic area were taken from Golgi-Cox stained brain tissue. Results reveal minimal effect of high-CBD low-THC strains on measures of activity, anxiety-like behaviour, fine motor function or spatial learning and memory. Cortical thickness and thalamic measurements will be discussed within the context of current literature. Funding: Natural Sciences and Engineering Research Council of Canada, Branch Out Neurological Foundation.

Speaker

Claire Niehaus MSc. Candidate, University of Lethbridge

Effects of repeated social defeat stress on effort-based decision-making behavior in adult male mice

Effects of repeated social defeat stress on effort-based decision-making behavior in adult male miceNishi, Mayumi, Endo, Nozomi, Somayam, Nami Dept. of Anatomy and Cell Biology, Nara Medical UniversityStress is a major risk factor for the development of psychiatric disorders such as depression, anxiety, and post-traumatic stress disorder. Repeated social defeat stress (RSDS) is commonly used as an ethologically relevant stressor in rodents. Recent numerous studies have shown that the influences of RSDS on depressive- and anxiety-like behaviors in mice. In this study, we examined effects of RSDS on effort-based decision-making behavior related to reward acquisition in mice by using our own behavioral test. In our protocol, C57BL / 6N mice were exposed to physical contact from aggressive ICR mice for 10 min a day in consecutive 10days. Then we performed social avoidance test and selected RSDS mice that exhibited 40% or more avoidance ratio to ICR mice in subsequent behavior test. Control mice had never been exposed to the physical attack of the ICR mice. Then, all mice were food restricted to approximately 85-90% of free-feeding weight before the behavior test. In the effort-based decision-making test, milk chocolate (20 mg) as

a high-reward and food pellet (25 mg) as a low-reward were placed in each side of the experimental box. A high wall was set upped as a high-effort in front of chocolate reward, and a low wall was set upped as a low-effort in front of the food pellet reward. Mice were allowed to freely select either high-reward/high-cost or low-reward/low-cost option, and mice have to overcome the higher wall to earn the high-reward. Control mice mostly selected high-effort/high-reward option (approximately 90 % of choice for chocolate). In contrast, RSDS mice were divided into two groups; RSDS mice that chose the comparable percent of high-effort/high-reward option as with control mice and RSDS mice that did not absolutely choose high-effort/high-reward option. Importantly, even RSDS mice that only chose low-effort/low-reward option remained motoric abilities to overcome the high wall. These findings suggest RSDS produces abnormal reward-cost ratios in effort-based decision-making in mice which causes individual differences in susceptibility to the same stress. We are now analyzing the neural mechanism of the effects of RSDS on effort-based decision-making behavior.Funding AcknowledgementKAKENHI JP (17H06060 and 17K19922 to MN, 17H07032 to NE)

Speaker

Mayumi Nishi Professor, Nara Medical University

Probiotic treatment affects maternal care quality and offspring wean weight in Long-Evans rats

Probiotic treatment affects maternal care quality and offspring wean weight in Long-Evans rats. O'Leary, M. Elizabeth 1, Myles, Elizabeth M. 1, Tompkins, Thomas A. 2 & Perrot, Tara S. 1, 3. 1 Department of Psychology and Neuroscience, Dalhousie University, 1355 Oxford Street, Halifax NS, B3M 4R2, Canada, 2 The Rosell Institute for Microbiome and Probiotics, Lallemand Health Solutions, Inc., 6100 Avenue Royalmount, Montreal QC, H4P 2R2, 3 The Brain Repair Centre, 1348 Summer Street, Halifax NS, B3H 4R2. Murine maternal care behaviours heavily influence the development of their offspring's stress response. These behaviours are affected by a variety of external factors, including nutrition. Therefore, we investigated the effects of probiotics on maternal care and subsequent offspring outcomes. We hypothesized that dams given probiotics throughout pregnancy and nursing would show increased maternal care, compared to placebo-treated dams. We also hypothesized that offspring from probiotic-treated dams would have a more moderate stress response than the offspring of placebo-treated dams. Dams were provided Lacidofil (a probiotic containing Lactobacillus rhamnosus R0011 and Lactobacillus helveticus R0052) for 42 days, and the daily frequency of maternal behaviour was monitored for the first postnatal week. Offspring were weighed at birth, weaning and before sacrifice. At sacrifice, offspring were exposed to predator stress, and plasma was collected to analyze stress hormones via multiplex ELISA. Maternal care data were analyzed via nonparametric t-test, weights and ELISA data were analyzed with two-way ANOVAs. Results provided partial support for our first hypothesis: probiotic-treated dams performed more arched-back nursing behaviour and trended towards higher licking/grooming behaviour, compared to placebo-treated dams. We found no support for our second hypothesis. Exploratory analyses showed that pups from probiotic-treated dams were significantly heavier at weaning than pups from placebo-treated dams. This study adds to the body of work regarding the factors that affect maternal behaviour and offspring development. On-going research is examining glucocorticoid receptors in these offspring, which represent a molecular marker of enhanced stress regulation that is influenced by maternal care. Funding: Mitacs Accelerate Fellowship, Natural Sciences and Engineering Research Council of Canada Engage grant, Rosell Institute for Microbiome and Probiotics.'‹

Speaker

Elizabeth O'Leary Dalhousie University

Concerted but segregated actions of OXT and AVP on different LS subnetworks determine

female aggression

Concerted but segregated actions of OXT and AVP on different LS subnetworks determine female aggressionVinÃcius Elias de Moura Oliveira1, Michael Lukas3, Hannah Wolf1, Elisa Durante1, Oliver J. Bosch1, Valery Grinevich4, Veronica Egger3, Trynke R. de Jong1,2, Inga D. Neumann1*1Department of Neurobiology and Animal Physiology, Behavioural and Molecular Neurobiology, University of Regensburg, Regensburg, Germany 2Medische Biobank Noord-Nederland B.V. Groningen, Netherlands3Department of Neurobiology and Animal Physiology, Neurophysiology, University of Regensburg, Regensburg, Germany 4Department of Neuropeptide Research in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, GermanyIn the context of aggression, females have been rarely studied in contrast to males. Knowing that i) rates of violence are rising among women, and ii) the neurobiology of aggression appears to be sex-specific, the development of new animal models is necessary to fully understand the neural underpinnings of female aggression. Here we established a novel and robust rat model of female aggression using a combination of social isolation and aggression training to enhance the mild levels of aggression displayed by group-housed female Wistar rats. Then, we specifically investigated the involvement of the endogenous oxytocin (OXT) and arginine vasopressin (AVP) systems during aggressive encounters, using neuropharmacological, opto- and chemogenetic as well as microdialyses approaches. We find that OXT release within the ventral lateral septum (vLS), as well as reduced AVP release within the dorsal LS (dLS), are required for female aggression. Accordingly, increased excitability of vLS neurons and decreased excitability of dLS neurons are shown to be essential to evoke aggression in females. Finally, using whole-cell voltage-clamp recordings we assessed the effects of these neuropeptides at the network level. Our results show that activation of OXT receptors in the vLS concomitantly decreases GABAergic spontaneous inhibition onto vLS neurons whereas increases it onto dLS neurons. Overall, our data indicate that the septal release of OXT and AVP affects female aggression by differential regulation of the excitatory-inhibitory balance within subnetworks of the LS.Funding acknowledgment: Neurobiology and Treatment of Adolescent Female with Conduct Disorder: The Central Role of Emotion Processing Fem-NATCD (602407)

Speaker

Vinicius Elias de Moura Oliveira Dr., University of Regensburg

SEX AND AGE DIFFERENCES IN ONE-TRIAL METHAMPHETAMINE SENSITIZATION IN SPRAGUE-DAWLEY RATS

Sex and age differences in one-trial methaphetamine sensitization in Sprague-Dawley rats. Omerjee, Faiyaz; Sortman, Bo; Moreno-Barriga; Cynthia, Nunez-Larios; Franco, Daniela; Zavala, Arturo; California State University, Long BeachMethamphetamine (METH) behavioral sensitization is a phenomenon in which previous administration to METH elicits a heightened behavioral response in subsequent exposures. Research has found that even one previous pairing is enough to elicit sensitization. In adult rats, sensitization is context-dependent, in which a sensitized response is only evident in the area in which they had previously received the drug. Juvenile rats (postnatal day [PD] 24 or younger), however, exhibit context-independent sensitization, a heightened response regardless of what environment the METH was previously paired. Adolescent rats (PD 25-50) do not exhibit sensitization to METH. Prior studies have examined a wide range of doses of METH (1-6 mg/kg), but doses lower than 1 mg/kg METH have not been used. Thus, the present study examined one-trial sensitization in juvenile, adolescent, and adult rats using 0.1 and 0.3 mg/kg of METH. During the pretreatment phase, PD 18, 28, 38, or 68 male and female rats were injected with saline or 3 mg/kg METH and placed in a novel activity chamber, where their locomotor activity (distance traveled in m) was assessed for 60 min. Rats were then taken to their home cage. 45 min later, a subgroup of rats that had been given saline in the activity chamber were then injected with 3 mg/kg METH and, placed back in their home cage. During the challenge test, PD 19, 29, 39, or 69 male and female rats were injected with saline or METH (0.1 or 0.3 mg/kg) before being placed in the activity chamber, during which distance traveled was assessed for 90 min. The results show that PD 29 and 39 adolescent male and female rats exhibited context-dependent sensitization. Interestingly, sex-related differences were observed as PD 39 female rats exhibited behavioral sensitization only when challenged with 0.3 mg/kg METH, while male rats exhibited behavioral sensitization only at 0.1 mg/kg METH. In contrast, PD 19 and 69 male and female rats did not exhibit behavioral sensitization at any dose.Acknowledgments: This research was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Numbers; UL1GM118979; TL4GM118980; RL5GM118978. The content is solely the responsibility of

the authors and does not necessarily represent the official views of the National Institutes of Health.

Speaker

Faiyaz Omerjee Supplemental Instruction Leader, California State University, Long Beach

Early Life Stress Increases Impulsive Action in Male but not Female Rats

Early Life Stress Increases Impulsive Action in Male but not Female Rats.Evelyn Ordoñes Sanchez, Charleanne Rogers, Miranda Langrehr, Alessandro Jean-Louis, Neil Sekhawat, James Flowers II, Cory S. Ardekani, & Debra A. Bangasser, PhDTemple UniversityEarly life stress can have detrimental effects on health and behavior that can persist into adulthood. Yet, how exactly early stressors can alter impulsive behaviors in adulthood and underlying biological mechanisms, is unclear. Here we tested how a rat model of early life stress can affect impulsivity in adult male and female rats. In order to induce stress in rats, our laboratory utilized the limited bedding/nesting (LBN) model. In LBN models, pups are reared in an environment with scarce bedding/nesting materials. This type of environment not only is stressful to the dam but can also be stressful to the developing pups. After pups endure a week of being in the LBN manipulation, they are returned to normal housing conditions and left undisturbed until adulthood. As adults, we can then measure whether LBN affects their impulsive actions. Impulsive actions are behaviors considered mistimed or premature. In order to measure impulsive actions in adult male and female rats, we utilized the Differential Reinforcement of Low Rate (DRL) task. DRL tasks measure the ability to withhold responses during a delay (e.g., 10 sec). If the response occurs before the delay is up, there is no reward and the trial restarts. Results from this study showed LBN males had significantly high burst responses (presses within 3 sec) during the first two days of training that later returned to control levels. Increased impulsivity was also detected when LBN rats were switched from the 5sec to 10 sec delay, as indicated by the overall increases in lever presses that returned to control levels after several days. LBN had no effect on female impulsive action. These results could suggest that although stressed males displayed elevated impulsivity initially, through continued training, stressed males were able to learn to modify their responses to reduce impulsive action to control levels. Future studies will focus on examining how ELS affects biological mechanisms associated with impulsivity.

Speaker

Evelyn Ordoñes Sanchez Graduate Researcher, Temple University

Discrimination of ICSS cues

Discrimination of ICSS cues. Pacheco-Gomez Benita 1, Velazquez-Martinez David 2. 1 Universidad Nacional Autonoma de Mexico, 2 Universidad Nacional Autonoma de Mexico. Keywords: ICSS cue, discrimination, dopamine. It has been reported that intracranial self-stimulation (ICSS) may serve as a discriminative stimulus. Few studies assessed the cues produced by intensity or frequency (but not both) of stimulation. Seven Long Evans rats were trained to discriminate between high and low intensity cues produced by electrical brain stimulation (ICSS) in the medial forebrain bundle (MFB) in the vicinity of lateral hypothalamus. Differential ICSS signaled the correct lever and only one response was required to obtain sucrose reinforcer. The high intensity cue was separated 0.6 log units from the low intensity cue, both delivered at 200 Hz. After attaining discrimination criteria (more than 80% accuracy to both high and low intensity conditions), generalization tests began. During intensity tests, the ICSS intensities were varied in 0.1 log steps but frequency (200 Hz) remained constant for all intensity parameters. On frequency generalization tests, frequency varied in 0.1 log decreasing steps at the high intensity. Lever selection was an intensity or frequency dependent function: the lowest intensity or frequency showed a similar discrimination index to the low training cue while the highest intensity or frequency produced a similar discrimination index to the high training cue. When a dose of 0.17 mg/kg of the dopamine agonist apomorphine was administered on the intensity generalization tests, a dose dependent parallel leftward

shift was observed. Results provide strong support about interchangeable intensity/frequency for excitation of the MFB bundle. Supported by GRANT DGAPA-IN307417.

Speaker

Benita Pacheco-Gómez Universidad Nacional Autónoma de México

The role of kappa-opioid receptors in conditioned fear learning in high vs. low alcohol drinking rats

Role of kappa-opioid receptors in conditioned fear in high vs. low alcohol drinking rats. Pajser, A., Fisher, H., & Pickens, C. Anxiety and alcohol use often co-occur in humans. In a laboratory setting, we also previously found an association between the amount of alcohol rats voluntarily consume and conditioned fear (higher drinking associated with lower fear). Because the opioid systems can affect both alcohol consumption and fear learning, we examined whether these individual differences in voluntary alcohol consumption and fear responding may be due to individual differences in the kappa-opioid system, by administering the kappa-opioid receptor antagonist LY2456302 (LY) before fear conditioning in high-, low-, and water-drinkers. Male and female Long-Evans rats received chronic intermittent alcohol access or water-only access for 6 weeks (PND 26-66). We divided the rats (based on drinking in the last 2 weeks of access) into high drinkers, low drinkers, or water drinkers (no alcohol access). Rats were food-restricted and received a single fear conditioning session 15 days after the final alcohol access period. Rats in each of the 3 drinking conditions received either a 10 mg/kg s.c. injection of LY or vehicle 2 hours prior to fear conditioning and were tested for conditioned fear two days later. Pre-training LY administration had no clear effect on fear expression during training or testing. However, there was a significant negative correlation between the amount of alcohol consumed across the 6 weeks of access and fear expression during the fear test for males that received pre-training LY (resembling our previous finding that high drinking rats had lower fear). We failed to replicate our prior findings of individual differences in alcohol consumption associated with conditioned fear in drug-free male rats, potentially due to a lack of early-life transportation stress in the current experiment (rats for previous experiments were purchased and shipped at weaning, but rats for the current experiment were bred in our facility). Future research will determine if early life stress may lead to alterations in the kappa-opioid receptor system, such that early life stress and kappa-opioid antagonism (in animals without early life stress) exhibit similar behavioral patterns. This project was supported by funds from Kansas State University, grant GM113109 from the National Institute of General Medical Science of the National Institutes of Health (C.L.P.)

Speaker

Alisa Pajser graduate student, Kansas state university

Interplay between estrogen and oxytocin receptors in the rapid mediation of social recognition

Interplay between estrogen and oxytocin receptors in the rapid mediation of social recognition. Pietro Paletta 1, Imanjit Grewal 1, Alicia Clarke 1, & Elena Choleris 1. 1 University of Guelph. Estrogens and oxytocin (OT) have been found to facilitate social recognition (SR). Knocking out the genes for the estrogen receptors (ER), OT, or the OT receptor (OTR) impairs SR, whereas administrations of 17b-estradiol (E2), agonists for the ERs, or OT can facilitate SR. From this research an interplay between the estrogen and OT systems in the mediation of SR was proposed. It was suggested that estrogens bind to the ERs in the paraventricular nucleus (PVN) of the hypothalamus, where most of the OT is produced in the mouse brain and will cause a release of OT into the medial amygdala (MeA), that receives olfactory information of conspecifics that are encountered. The OT released into the MeA will bind to the OTR to facilitate SR. Our previous research into this model has revealed that the infusion of E2 into the PVN can rapidly facilitate SR and that this facilitation is blocked by an OTR antagonist (OTRA) in the MeA, a subeffective dose that by

itself is not able to block SR. These findings show support for the idea of the interplay between the estrogen and OT systems in the mediation of SR. Our current experiments are aimed at determining which ER is mediating this effect. This was done first by infusing specific ER beta (ERb) and the G-protein couple ER (GPER) agonists, DPN and G1, into the PVN. We found that both agonists were able to rapidly facilitate SR at the two highest doses. We are now determining if the infusion of the OTRA in the MeA can block the rapid facilitation of SR by either agonist, as this will reveal which ER is mediating the interplay between estrogens and OT. The most effective dose of each agonist will be infused into the PVN with the subeffective dose of the OTRA infused into the MeA. A rapid SR paradigm will then be used where 2 stimulus mice are introduced to the experimental mouse for 2 sample phases, followed by a test phase where one of the stimulus mice from the sample phases and a novel stimulus mouse will be presented. If the novel mouse is investigated more than the previously seen stimulus mouse, it suggests that they recognize that mouse and SR occurred. If it is found that the OTRA blocks the effect of either ER agonist, it suggests that that ER mediates the interplay between estrogens and OT on SR. Funded by NSERC.

Speaker

Pietro Paletta PhD Candidate, University of Guelph

The effects of acute finasteride treatment in MK-801-treated mice

The effects of acute finasteride treatment in MK-801-treated miceParathy, Nageiswari1, Wong, Alanna2, Groenewoud, David3, Mak, Hui Min1, Wong, Peiyan1,4, Dawe, Gavin11Department of Pharmacology, National University of Singapore, Singapore2Department of Pharmacy, National University of Singapore, Singapore;3Department of Biological Sciences, National University of Singapore, Singapore;4Neuroscience and Behavior Disorders Programme, Duke-NUS Medical School, SingaporeBackground and Objectives: Schizophrenia is a neuropsychiatric disorder that presents itself in the form of positive and negative symptoms such as hallucinations, delusions and social withdrawal along with cognitive impairment. While treatments with antipsychotic drugs have shown promise in reducing the positive symptoms, there are no current solutions to aid in the alleviation of negative symptoms and cognitive impairment. In recent years, altered neurosteroid levels in the brain have been implicated as a possible biological basis of schizophrenia. Synthesis of these neurosteroids is highly regulated by enzymes, including the 5-Î± reductase enzyme that has increasingly been identified to be involved in schizophrenia. Here, we studied the effects of finasteride, a 5-Î± reductase inhibitor on the MK-801-treated mouse model. MK-801 is an N-methyl-D-aspartate (NMDA) antagonist and this mouse model can re-capitulate certain symptoms of schizophrenia, such as locomotor hyperactivity, stereotypy and impairments in sensorimotor functions. Methods: MK-801-treated (0.05 and 0.1mg/kg) wild-type (WT) mice were treated acutely with different doses of finasteride (25 and 50mg/kg) or vehicle before the behavioural effects of finasteride were characterised through open field test (OFT) for locomotor activity and pre-pulse inhibition (PPI) for sensorimotor gating. Results: Acute treatment with finasteride was able to normalize locomotion and partially rescue sensorimotor gating functions in MK-801-treated WT mice to that of vehicle-treated WT mice. Conclusion:Our results suggest that acute finasteride treatment can rescue certain symptoms of schizophrenia in a preclinical mouse model of schizophrenia, warranting more investigation into the effects of finasteride in other mouse models of schizophrenia and the effects of other potential antipsychotics in the MK-801-treated mouse model. Acknowledgements: This work was supported by the NMRC NUHS Centre Grant - Neuroscience Phenotyping Core (NMRC/CG/M009/2017_NUH/NUHS)

Speaker

Nageiswari Parathy Research Assistant, National University of Singapore

The role of the ventral hippocampal-accumbens shell circuit in cued approach-avoidance decision making

The role of the ventral hippocampal-accumbens shell circuit in cued approach-avoidance decision making. Patterson, Dylan 1; Sassaninejad, Kian 2; Khan, Nisma 2; Ito, Rutusuko 1,2. 1 Department of Cell and Systems Biology, University of Toronto, ON, Canada, 2 Department of Psychology, University of Toronto Scarborough, Toronto, ON, Canada. Approach-avoidance conflict decision making is critical for survival and requires the effective evaluation of stimuli with mixed outcomes (positive and negative). Recent evidence has implicated the ventral hippocampus (vHPC) and nucleus accumbens (NAc) in the regulation of approach-avoidance conflict resolution. This study aimed to extend this finding by investigating the functional connectivity between the CA1 subregion of the vHPC and NAc in learned approach-avoidance decision making. To achieve this, rats were surgically injected with inhibitory DREADDs (AAV-CAMKIIa-hM4Di-mCherry) or a control vector (AAV-CAMKIIa-GFP) into the vCA1 and implanted with guide cannulae over the NAc shell to enable clozapine-N-oxide (CNO, 1mM) or saline to be infused directly into the NAc during testing. Rats were then trained in two customized behavioural tasks (Y-maze and operant) to associate visual-tactile or auditory cues with different outcomes: reward, shock, or no outcome (neutral). In the Y-maze, rats underwent Pavlovian conditioning to acquire the cue-outcome associations. In the operant box, rats learned to lever press for reward or withhold lever pressing for a foot shock or no outcome in the presence of different cues. Following successful learning, rodents underwent a conflict test in which the presentation of the aversive and appetitive cues were superimposed to elicit approach-avoidance conflict. In the presence of this motivational conflict, chemogenic inhibition of the vCA1-caudal NAc shell circuit resulted in increased time spent in the central hub during the Y-maze conflict task. This behaviour was accompanied by an increase in latency, retreats and risk assessment behaviour prior to entering the conflict or neutral arm. Furthermore, these effects occurred independently of alterations in locomotion, anxiety, conditioned cue preference or cue avoidance. In contrast, there was no effect of circuit inhibition in the operant version of the task. Our findings implicate the vCA1-caudal NAc shell circuit in facilitating the decision to approach in the face of cued motivational conflict. This work was funded by CIHR and SSHRC.

Speaker

Dylan Patterson MSc Student, University of Toronto

Physical, cognitive and behavioral alterations in the adult offspring of CD-1 mice fed with a western diet during pregnancy and lactation

Physical, cognitive and behavioral alterations in the adult offspring of CD-1 mice fed with a western diet during pregnancy and lactation Pedraza-Medina, Ricardo 1,2; Cortes-Ãlvarez, Nadia 1,2; Pinto-GonzÃ¡lez, Fernanda 1,2; Moy-LÃ³pez, Norma 1; GuzmÃ¡n-MuÃ±iz, Jorge 1; Collas-Aguilar, Jorge 1. 1 Laboratorio de Neurociencias, Facultad de PsicologÃa, Universidad de Colima, Mexico; 2 Facultad de Medicina, Universidad de Colima, MexicoWestern diet (WD) has been described as the set of processed foods, which are high in calories, fat and sugar, low in fiber, but pleasant in taste and texture. Its consumption seems to affect physical, physiological and behavioral parameters. Therefore, its consumption during pregnancy and lactation could affect neurodevelopment in the offspring impairing different indicators in the adulthood. The aim was to evaluate the physical, cognitive and behavioral effects in the offspring of CD-1 mice fed with a WD during pregnancy and lactation. Thirty-six mice were used, 18 from mothers fed a WD, and 18 from mothers fed a control diet during pregnancy and lactation. Weight gain, food intake of mothers and weight gain in the offspring were registered. At postnatal day (PD) 90 and 180, offspring were evaluated in the Open Field Test (OFT) and Morris Water Maze (MWM). In dams, consumption of a WD increased calorie intake during pregnancy and lactation ($p<0.05$); in the offspring, experimental group showed a rise in BMI ($p<0.001$) and weight ($p<0.001$) at birth, during the first week of life this group maintained increased weight ($p<0.001$). Moreover, there were no changes in mobility or learning at PD90 or 180. WD impaired memory ($p<0.05$) at PD90 but not at PD180, and increased anxiety-like behavior ($p<0.005$) at PD 90 and 180. In conclusion, WD consumption during pregnancy and lactation alters growth indicators as BMI and weight gain during early stages of development, cognitive modifications as memory impairments during young adulthood, while behavioral anxiety-like behavior persist altered until adulthood. Furthermore, even after the physical and cognitive consequences become non-significant, the behavioral consequences still present.

Speaker

Ricardo Pedraza-Medina B. S. in Psychology, Universidad de Colima

Bench to Bedside and Back: A Longitudinal Translational Study of Motor Outcome Measures in Individuals and Preclinical Models of Angelman Syndrome

Bench to Bedside and Back: A Longitudinal Translational Study of Motor Outcome Measures in Individuals and Preclinical Models of Angelman SyndromePetkova, SP1, Duis J2*, and Silverman, JL1*1Dept. of Psych., MIND Institute, Uni. of California Davis 2Dept. of Ped., Uni. of ColoradoAngelman Syndrome (AS) is a genetic neurodevelopmental disorder characterized by developmental delay, lack of speech, seizures, intellectual disability, and walking and balance disorders. We have focused on motor ability as an outcome measure as movement disorders including uncoordinated limb movement, delayed and abnormal walking and postural movements affect nearly every individual with AS. Motor outcomes present a strong opportunity for direct translational studies to investigate pharmacological, dietary, and genetic therapies. Clear phenotypes have been widely published on these phenotypes clinically (Wheeler et al., 2017) and preclinically (Born et al., 2017; Berg et al., 2020). One pilot study in children with AS showed abnormal and stunted walking compared to an age matched typical developing group (Grieco et al. 2018). To date, gait studies have not been reported in any preclinical model of AS. To fill this gap, we investigated temporal and spatial gait parameters in wild-type (WT) (N=30) and AS mice (N=20) from weaning to 6 months of age. We compared our results to findings using the ActiMyo system in AS patients from ages 4-11 in a clinical setting and in their home environment. We utilized the DigiGait treadmill system and observed deficits such as a wide unstable stance, increased stride length, decreased stride frequency, and altered stride dynamics, compared to WT controls. DigiGait does not rely on context novelty so there was no effect of test-retest, making it an ideal outcome for within-subject therapeutic testing. We found that abnormal gait dynamics observed at adulthood became apparent by day 30 and continued to worsen over time. Clinical data with the ActiMyo showed that individuals with AS are unable to reliably adapt their gait to natural environments predisposing them to falls. Future experiments will look at neonatal milestones to investigate earlier onsets of low motor abilities. Our results reflect the first longitudinal studies in preclinical and clinical AS work, investigating developmental gait trajectories in a disease model. This is a critical discovery of a reliable outcome measure for the numerous therapeutic approaches being tested for AS.

Speaker

Stela Petkova MIND Institute, University of California, Davis

APOE genotype, sex, and ovariectomy influence anxiety-like behaviors in an EFAD mouse model of Alzheimer's Disease

APOE genotype, sex, and ovariectomy influence anxiety-like behaviors in an EFAD mouse model of Alzheimer's disease. Sarah M Philippi 1, Lisa R Taxier 1, Jason York 2, Mary Jo LaDu 2, and Karyn M Frick 1. 1 University of Wisconsin-Milwaukee. 2 University of Illinois at Chicago. Symptoms of anxiety occur in 50-75% of Alzheimer's disease (AD) patients and increase throughout disease progression. APOE4 genotype, the leading genetic risk factor for AD, may influence symptoms of anxiety in AD patients. Women APOE4 carriers are at greatest risk of developing AD, perhaps due in part to estrogen loss after menopause. However, contributions of APOE4 genotype, sex, and estrogen loss to anxiety in AD remain unclear. Effects of APOE status, sex, and ovariectomy (OVX) on anxiety-like behaviors in an open field were measured. First, effects of sex and APOE genotype were examined in gonadally-intact transgenic male and female mice expressing 5 familial AD mutations (5xFAD+/-) and human APOE3+/+ (E3FAD) or APOE4+/+ (E4FAD). We next examined effects of APOE genotype and OVX in female EFADs. Mice were trained in object recognition (OR) and object placement (OP) tasks. Anxiety-like behaviors were measured using open field (OF) data collected during the first habituation trial of OR or OP testing, during which mice had 5 minutes to explore an empty box. Total distance traveled, average speed, and time spent in the center of the apparatus were measured. Sex influenced total distance and average speed, such that females traveled further at faster speeds than males. Only APOE genotype affected the time spent in the center of the OF apparatus, with E3FADs spending more time in the center than E4FADs, regardless of sex. OVXed E3FADs exhibited similar anxiety-

like behaviors as both intact and ovariectomized E4FADs. E3FADs spent more time in the center of an OF than E4FADs of both sexes, suggesting an association between APOE4 and increased anxiety-like behavior. OVX increased anxiety-like behaviors in E3FADs to similar levels observed in intact and OVXed E4FADs, suggesting that the loss of estrogens in E3FAD females heightens anxiety-like behaviors. These findings suggest significant interactions among APOE genotype, sex, and estrogens that may influence the incidence of anxiety in women with AD. Support for this project was provided by the Alzheimer's Association (SAGA-17-419092), NIH (R01MH107886), and from UWM SURF and SERA awards.

📢 **Speaker**

Sarah Philippi Research Technician, University of Wisconsin - Milwaukee

The Role of PDE11A4 in Age-Related Decline of Social Memories

The role of PDE11A4 in age-related decline of social memories. Katy Pilarzyk, Neema Patel, Abigail Smith, and Michy P. Kelly, Ph. D. Department of Physiology, Pharmacology, and Neuroscience, University of South Carolina School of Medicine.Associative memories (aMEMs) are more susceptible to age-related cognitive decline than are recognition memories for reasons that are not well understood. Age-related increases in phosphodiesterase 11A (PDE11A), an enzyme that breaks down cAMP/cGMP and regulates social behaviors, may be a fundamental mechanism underlying age-related decline of aMEMs. PDE11A4 is almost exclusively expressed in the ventral hippocampal formation (VHIPP), a brain region key to many types of aMEMs. cAMP/cGMP signaling is decreased in the aging and demented hippocampus (HIPP), which is consistent with our recent observations of aging/dementia-related increases in HIPP PDE11A4. Specifically, we observe a selective increase of PDE11A4 in the membrane compartment of the VHIPP. We have seen significantly elevated PDE11A4 in HIPP of demented vs. non-demented aged humans with a history of TBI. We hypothesized that age-related increases in HIPP PDE11A4 occur in a compartmentalized manner and impair social associative long-term memories (aLTMs). To test this hypothesis, we 1) prevented age-related increases in PDE11A4 using a Pde11a KO mouse, 2) reversed age-related increases in membrane PDE11A4 by disrupting PDE11 homodimerization and, 3) mimicked age-related increases in PDE11A4 by virally overexpressing PDE11A4 in the HIPP of old Pde11a KO mice. We found that while WT mice demonstrate age-related cognitive decline of remote aLTM, old KO mice show robust remote aLTM. Further, disrupting PDE11A4 homodimerization in old WT mice was sufficient to reverse age-related increases in PDE11A4 expression/accumulations and rescue age-related decline of social LTMs. Lastly, mimicking age-related increases in PDE11A4 expression in the HIPP of old KO mice was sufficient to cause aging-like deficits of social LTMs. Consistent with findings of aged humans with a history of TBI and dementia, the combination of aging and surgery in mice impairs both aLTMs and social recognition LTMs when PDE11A4 is present. These data suggest that reversal/mimicry of age-related increases in HIPP PDE11A4 expression is sufficient to rescue/cause deficits in social aLTMs and the combination of PDE11A4 and TBI may accelerate age-related cognitive decline to dementia. NIA Grant R01AG061200

📢 **Speaker**

Katy Pilarzyk PhD Candidate, University of South Carolina- School of Medicine

The Expression of Membrane and Nuclear Sex-Hormone Receptors during Early Development of Hippocampus

The expression of the membrane and nuclear sex-hormone receptors during early development of hippocampus PillerovÃ¡, Miriam1; RenczÃ©s, Emese1; VlkovÃ¡, Barbora1; Celec, Peter1; TÃ³thovÃ¡, Ä½ubomÃra1; Hodosy, JÃºlius1,21 Institute of Molecular Biomedicine, Faculty of Medicine, Comenius University, Bratislava, Slovakia2 Institute of Physiology, Faculty of Medicine, Comenius University, Bratislava, SlovakiaSex-hormones influence the early development of the hippocampus. While the genomic effects of androgen (AR) and estrogen (ERÎ±, ERÎ²) nuclear receptors are relatively well examined, the physiological

importance of rapid, non-genomic effects of activation of membrane steroid receptors is not well known. The main aim of our study was to monitor the expression of GPER1 and ZIP9, membrane receptors for estrogens and androgens, respectively, during the early stage of hippocampus development. Blood samples and samples of the hippocampus were collected from healthy Wistar rats (n=68) in postnatal days (PND) 1, 7, 14, and 21. Relative gene expression was analyzed using RT-qPCR with PPIA as the reference gene. Plasma testosterone concentration was measured using ELISA. The concentration of testosterone continuously increased in time in both sexes, although, males had a higher concentration of testosterone on PND 7. AR expression was 50% higher on PND 7 and PND 14 in comparison to PND 1 and PND 21 in both females and males. In males, ERÎ² expression continuously increased. The expression of ZIP9 influenced neither the sex nor the development stage. In males, GPER1 expression was 2-fold higher on PND 21 in comparison to PND 1-14.The described dynamics of AR, ERÎ², and GPER expression, together with the increasing circulating testosterone, could be important for both the physiological development of the hippocampus in rats and for research of neurodevelopmental disorders in animal models. Other studies are needed to elucidate the importance of membrane steroid receptors and sex differences in the sensitivity of the hippocampus to androgen/estrogen signaling.This study was funded by APVV grant No. APVV-15-0045.

Speaker

Miriam Pillerova Uwm

Modeling behavioral therapeutic approaches for major depression disorder (MDD): the impact of effort-based reward (EBR) training on attentional and plasticity processes in male and female rats.

Modeling behavioral therapeutic approaches for major depression disorder (MDD): the impact of effort-based reward (EBR) training on attentional and plasticity processes in male and female rats.E. Ploppert, J. Jacob, A.Deutsch, S.Watanabe, K. Gillenwater, K. Lambert. Department of Psychology, University of Richmond, Richmond VA US. Though current research points toward the effectiveness of cognitive/behavioral therapies in building resilience against the emergence of depressogenic symptoms, a lack of appropriate animal models for behavioral therapies has presented a bio-medical translational barrier to understanding the neurobiological mechanisms associated with treatment outcomes. In the current study, a rodent model utilizing contingency-training was used to explore behavioral training effects on cognitive strategies associated with emotional resilience. Using the EBR model, male and female rats were assigned to either an EBR contingent-trained group or a non-contingent trained group (n=10 for each group; N=40). Following 7 weeks of training focused on building associations between physical effort (digging) and desired outcomes (food reward), animals were assessed for evidence of emotional, cognitive and neurobiological resilience. In a pattern separation task assessing attention directed toward varying degrees of pattern divergence, EBR-trained animals exhibited a significantly shorter latency to the altered stimulus in the most challenging phase of assessment (i.e., 6% pattern change; p=.023), suggesting that EBR training enhanced vigilance for subtle environmental changes in this task. Assessment of brain-derived neurotrophic factor expression indicated no training effects in the hippocampal dentate gyrus and CA1 areas. Because activation of the lateral habenula has been implicated in MDD symptoms, it is interesting that a non-significant trend of lower activation was observed in the EBR-trained animals (p=0.125). In contrast to previous work, EBR training had no effect on endocrine measures; however, females exhibited a significantly higher DHEA/CORT ratio, a marker of emotional resilience. Histological analyses of various neuroplasticity markers, including Golgi-stained neuronal parameters and doublecortin, Ki-67, and NMDA receptor-immunoreactivity are in progress. More research is necessary to discern the neurobiological mechanisms of EBR-driven cognitive and behavioral modifications. Funding supported by NIMH 1R15MH117628-01A1 to KGL.

Speaker

Emily Ploppert Research Assistant, University of Richmond

Effect of Toluene Chronic Exposure on Exploratory Behavior and Recognition Memory in Different age Rats

Effect of Toluene Chronic Exposure on Exploratory Behavior and Recognition Memory in Different age Rats N. O. Pochkhidze 1,2, M. G. Zhvania 1,2, N. J. Japaridze 2, Lomidze N.1 1. Institute of Chemical Biology Ilia State University, Tbilisi, Georgia 2. I. Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgianino.pochkhidze.1@iliauni.edu.geToluene and toluene-containing volatile substances are the most widely abused solvents with demonstrative addictive potential in humans. Several data indicate that as a result of toluene misuse alterations in learning and memory in organisms of different age take place. But because of differences in species, length of exposure, dose or rate of administration, it is not always possible to conclude whether adolescent experience results in changes in learning and memory are comparable to that seen in adults. The present study has been undertaken to determine whether toluene chronic exposure provokes immediate and/or persisting effect on exploratory behavior and recognition memory in open field in adolescent and adult rats. We exposed male Wistar rats at ages P 28-32 (adolescents) and P 70-75 (adults) to 2000 ppm inhaled toluene for 40 days. The immediate and persisting effects of toluene misuse (immediately after the end of toluene chronic inhalation and 90-day after the end of toluene chronic inhalation, correspondingly) were evaluated. Experimental protocol was approved by Animal Studies Committee of I. Beritashvili Center of Experimental Biomedicine. The major findings are: (1) toluene misuse alters exploratory activity and recognition memory in adolescent and adult rats; (2) the level of alterations depends upon the postnatal age of testing animals. In particular: in adolescent rats the most significant behavioral alterations were observed by the day following toluene chronic exposure. These alterations do not progress significantly during abstinence period: some altered parameters were almost the same as observed the day following immediately after toluene misuse and others were very close to observed in control animals. Therefore, in adolescent rats the most expressed was immediate effect of toluene misuse. Contrary to it: in adult rats most alterations significantly progress during 90 d period of abstinence. So, in these animals more substantial was persistent effect of toluene chronic exposure. On the bases of our data it is possible to suggest that adolescent rats may show partial recovery from once the toluene toxic effect no longer persists.

Speaker

Nino Pochkhidze PhD Student and Researcher, Ilia State University; I.Beritashvili center of Experimental Biomedicine

Assessment of ultrasonic vocalisations of isolated pups in the valproic acid model of autism

Assessment of ultrasonic vocalisations of isolated pups in the valproic acid model of autismPotasiewicz, Agnieszka; Kuziak, Agata; Popik, Piotr; Nikiforuk, Agnieszka.Department of Behavioral Neuroscience and Drug Development, Maj Institute of Pharmacology, Polish Academy of Sciences, Cracow, PolandBackground: Autism spectrum disorder (ASD) is most likely of a neurodevelopmental nature and its symptoms are often evident from an early age. Its core symptoms include disturbed social behaviour, disturbed social communication and stereotypical behaviour. Prenatal exposure to the anticonvulsant valproic acid (VPA) medication is associated with an increased risk of ASD in humans and yields an autistic-like phenotype in rodents. The aim of the present study was to examine the effects of prenatal valproic acid (VPA) treatment on the level of communication in pups during the separation from the mother.Materials and methods:Sprague-Dawley rat dams received a single, intraperitoneal injection of VPA (500 mg/kg) or vehicle on 12.5 day of pregnancy. On postnatal day 6, the pups ultrasonic vocalisation (USVs), evoked by isolation from mother, were recorded for 3 minutes. Stress factor (the measurement on familiar/unfamiliar bedding) was included in the USVs analysis. Results:The results demonstrate that both control and VPA-treated pups emitted greater numbers of longer USVs on the unfamiliar bedding as compared with familiar bedding conditions. As compared to the controls, VPA male and female pups displayed: i) the lower number of USVs, ii) the shorter USV duration and, iii) the greater peak frequency. Call type distribution did not differ between all tested groups.Conclusions:The present study demonstrates that VPA-exposed pups display impaired social communication (reduced number and duration of USVs).Acknowledgements: This study was supported by the Polish National Science Centre grant NCN 2016/23/B/NZ7/01131 and by the Statutory funds of the Maj Institute of Pharmacology, Polish Academy of Sciences.

Speaker

Agnieszka Potasiewicz post-doc, Maj Institute of Pharmacology of the Polish Academy of Sciences

In vivo striatal dopamine dynamics during stimulus-response learning

Oren Princz-Lebel, Miguel Skirzewski, Amy C. Reichelt, Danial Palmer, Marco A.M. Prado, Vania F. Prado, Penny A. MacDonald, Lisa M. Saksida & Timothy J. Bussey

Habits provide a rapid, efficient means for decision-making by permitting common behaviours to be executed more automatically on the basis of their past success. Many psychiatric and neurodegenerative disorders are characterized by aberrant decision-making and dysfunctional habit formation, with behavioural deficits often seen in Huntington's and Parkinson's disease, and overreliance often observed in addiction and obsessive-compulsive disorders. Dorsal striatum neurocircuitry is known to underlie the habitual control of behaviour by facilitating synaptic plasticity and strengthening stimulus-response associations. One essential neurotransmitter that regulates activity within the dorsal striatum is dopamine, and a loss of modulatory control of striatal dopamine has been shown to impact the rate of habit formation and associated processes. How the dynamic interplay of neuroplasticity across the dopaminergic circuitry guides the acquisition of habits, and whether these dynamics differ across dorsal striatum subregions remains unknown. Here, we uniquely combined automated touchscreen cognitive assessments, fibre photometry, and the recently developed genetically-encoded dopamine biosensor, GRABDA, to record in vivo dopamine dynamics across the dorsal striatum while mice performed a Visuomotor Conditional Learning Task'"an established cognitive task which measures habit formation. Our preliminary results suggest that dopamine transients across the dorsal striatum respond dynamically to diverse behavioural events across learning, but these response patterns do not differ topographically.

Speaker

Oren Princz-Lebel PhD Student, University of Western Ontario

HIV-1 Tat promotes age-related cognitive and behavioral deficits in mice that are moderated by aging endocrine status

HIV-1 Tat promotes age-related cognitive and behavioral deficits in mice that are moderated by aging endocrine statusAlaa N. Qrareya1, Fakhri Mahdi1, Marc Kaufman2, Nicole M. Ashpole1,3, Jason J. Paris1,31Dept. of BioMolecular Sciences Dept., University of Mississippi 2The McLean Hospital Dept. of Psychiatry, Harvard University3Research Institute of Pharmaceutical Science, University of MississippiDysfunction of the hypothalamic-pituitary-gonadal axis is a common co-morbidity among HIV-1-infected individuals. This incidence is greater among those over the age of 45, who comprise ~60% of the U.S. HIV+ population. The underlying mechanisms are unknown, but both combined antiretroviral therapeutics or HIV-1 proteins, such as the trans-activator of transcription (Tat), are associated with dysregulation of lipid storage/synthesis or mitochondrial function. Few studies of Tat-mediated behavioral deficits in aged animals exist and the work that has been done has not been stratified by endocrine status. We anticipated that conditional Tat expression in aged transgenic mice (Tat+ mice) would impair cognition performance, increase anxiety-like behavior, allodynia, thermal hyperalgesia, and the incidence of age-related co-morbidities compared to age-matched controls (Tat- mice). We further expected aged females that maintained their reproductive status (pre-estropausal) to be more resilient to Tat/age-related co-morbidities than those that had transitioned to reproductive senescence (post-estropausal). Tat+ males demonstrated greater anxiety-like behavior on an elevated plus maze compared to Tat- control males and post-estropausal mice demonstrated greater anxiety-like behavior in an open field and an elevated plus maze compared to pre-estropausal females. Tat exposure decreased spatial memory performance in a radial arm water maze among males and post-estropausal females. Moreover, Post-estropausal females had poorer spatial memory performance that did their pre-estropausal counterparts. There was a main

effect for Tat to increase allodynia among all mice. When assessing endocrine function, Tat+ post-estropausal females had increased circulating corticosterone compared to their Tat- counterparts. Tat exposure increased circulating estradiol in males but decreased it in post-estropausal females. Thus, endocrine status may be an important predictor in Tat/age-related decline.AcknowledgmentsNIDA (R00 DA039791), NIGMS (P30GM122733), The University of Mississippi

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Speaker

Alaa Qrareya The University of Mississippi

Activation of serotonin input to the dorsal BNST leads to sex differences in fear learning

Activation of serotonin input to the dorsal BNST leads to sex differences in fear learning. R.Ravenelle 1, H. Yoon 2, E. Likhtik 3,1, N.S. Burghardt 2,1. 1.CUNY-Graduate Center, 2.Hunter College, Psych., 3.Hunter College, Biol. Women are twice as likely as men to be diagnosed with post-traumatic stress disorder (PTSD)- a disorder characterized by intense fearful memory formation. The neurobiological underpinnings of this sex difference are unknown. Given that serotonin (5-HT) dysfunction is implicated in PTSD, and 5-HT modulates fear learning, we are investigating whether 5-HT neurotransmission plays a role in this sex difference using auditory fear conditioning. The selective serotonin reuptake inhibitor citalopram or saline (10mg/kg or 20mg/kg, i.p.) was given 1hr prior to fear conditioning (5 tones co-terminated with a footshock). During recall testing 24hr later, the high dose of citalopram enhanced fear memory in both sexes, whereas the low dose only enhanced fear memory in females, suggesting females are more sensitive to 5-HT increases. A subset of mice were perfused 90min after training for immunohistochemical analysis of the neuronal activity marker c-Fos and the 5-HT2C receptor. At the low dose, females had elevated c-Fos levels in the dorsal bed nucleus of the stria terminalis (dBNST) and the central nucleus of the amygdala (CeA) compared to males. We then tested whether selectively enhancing 5-HT in the dBNST alone is sufficient to induce a sex difference in fear learning. 5-HT inputs to the dBNST were optogenetically stimulated using TpH2-ChR2-EYFP mice, in which channelrhodopsin is expressed exclusively on 5-HT neurons. During fear learning, 5-HT terminals were stimulated in the dBNST during tone presentations, and memory was tested 24hr later. 5-HT stimulation led to stronger fear memory in females but not males, further confirming enhanced sensitivity to serotonin in females in the dBNST. We are currently testing whether 5-HT release in the dBNST during fear conditioning differentially affects activation of 5-HT2C containing neurons across sexes, and are using awake-behaving electrophysiology to characterize dBNST-CeA circuit communication in a hyperserotonergic state. FUNDING: NIMH R21MH114182 (NB,EL), NIMHD of NIH G12MD007599 (NB) and PSC-CUNY (NB,EL).

Speaker

Rebecca Ravenelle PhD Candidate, City University of New York - Graduate Center

Wakeful quiescence: Awakening the influence of oxytocin on sleep-wake behaviour.

Wakeful quiescence: Awakening the influence of oxytocin on sleep-wake behaviour. Joel S Raymond 1, Nicholas A Everett 1, Anand Gururajan 1, Michael T Bowen 1.1The University of Sydney, Brain and Mind Centre, Sydney, Australia. Oxytocin is a versatile neuropeptide implicated in diverse range of neurobehavioural processes such as stress, social behaviour, and feeding. Based on the anxiolytic, serenic effects of oxytocin, one could posit that oxytocin should prime the brain for sleep and elicit hypnogenic effects. However, as the social salience hypothesis suggests that oxytocin promotes prosocial behaviour and directs attention toward social stimuli, oxytocin may be implicated in promoting wakefulness. To-date, little research has comprehensively investigated the role of oxytocin in sleep-wake behaviour and no explanation to reconcile these two seemingly competing hypotheses has been proposed. The current preclinical study investigated the dose-response relationship of oxytocin with sleep outcomes using radiotelemetry-based polysomnography in adult male Wistar rats. Oxytocin (0.1, 0.3 and 1 mg/kg) was

administered via the intraperitoneal route, and intraperitoneal caffeine (10 mg/kg) was also administered as a wake-promoting positive control. In rats, oxytocin demonstrated dose-dependent effects on sleep-wake behaviour: oxytocin initially promoted wakeful quiescence (a restful but conscious state) at the cost of reducing both active wakefulness and sleep. More specifically, oxytocin reduced NREM sleep during the 1-1.5 hours post-administration, and dose-dependently delayed REMS onset and reduced the proportion of time spent in REM sleep. This appears to reconcile the two competing hypotheses: in rats, oxytocin appears to promote a state of wakeful quiescence'"one of rest and relaxation, but also of responsive consciousness to environmental stimuli. Future research will elucidate the neurobiological underpinnings that mediate these oxytocin-induced effects on sleep outcomes.

Speaker

Joel S Raymond PhD Candidate, Brain and Mind Centre, The University of Sydney

Context for hunger: evaluating the role of ghrelin and AgRP neurons in context-conditioned overeating in mice.

Context for hunger: evaluating the role of ghrelin and AgRP neurons in context-conditioned overeating in mice. Reed F 1, Makdsi C 1, Lockie S 1, Andrews, Z 1.1Department of Physiology, Monash University, Victoria, Australia. Context presents an important factor in learned over-eating. When sated rats and mice are re-exposed to contexts in which they were previously hungry, they exhibit avid over-eating compared to mice that were never hungry. This suggests a key role of hunger circuits in regulating context-conditioned feeding behaviour. Hunger is mediated by two key mechanisms in the brain: via increased levels of ghrelin as well as increased activation of Agouti-related peptide (AgRP) neurons in the arcuate nucleus (Arc). Therefore, the aim of this study was to investigate the contribution of each of these hunger signals in context-conditioned feeding behaviour. We used a context-induced feeding paradigm that has previously been shown to require fasting to precipitate a conditioned feeding response. Briefly, mice were exposed to two novel contexts on the first day. The following two days mice re-entered one of the contexts for 30 minutes in the presence of palatable Froot Loops (CTX+), under sated conditions or conditions of simulated hunger (ghrelin i.p. (1mg/kg) or AgRP stimulation). On the test day, mice were exposed to the previously food-paired context (CTX+) and the non-paired context (CTX-) in a counterbalanced order, and Froot Loop consumption was measured in each. We show that ghrelin (1mg/kg, i.p) is sufficient to cause a robust feeding response during training, that are associated with significantly increased Froot Loop consumption in CTX+, when tested the following day in a sated condition. Next, using DREADDs (HM3Dq) and optogenetics (channelrhodopsin; ChR2 + unilateral fiber optic) within the Arc of AgRP-IRES-cre or WT mice, we assessed the role of AgRP signalling. AgRP-HM3Dq activation resulted in a robust feeding response during training, however, no preference for froot loops in CTX+ was apparent when tested the following day. AgRP-ChR2 mice ate significantly more than controls in CTX+ during training, but in contrast to sustained activation with DREADDs, they additionally formed a conditioned-feeding response: eating more than their WT counterparts in CTX+ compared to CTX-. This study shows that both ghrelin and AgRP signalling are sufficient for context-conditioned feeding behaviour, and highlights the important role of temporal specificity for AgRP activation in forming conditioned associations.This research was supported by an NHMRC grant awarded to S. Lockie & Z. Andrews, and a government research training program scholarship awarded to F. Reed.

Speaker

Felicia Reed

Manipulation of hippocampal perineuronal nets can bidirectionally modulate dietary-obesity induced memory impairment

Manipulation of hippocampal perineuronal nets can bidirectionally modulate dietary-obesity induced

memory impairment.

Reichelt, Amy 1,2, Bussey, Timothy, 1, Saksida, Lisa, 1. 1. Physiology and Pharmacology, Schulich School of Medicine and Dentistry, Western University, London, Canada. 2. Florey Institute of Neuroscience and Mental Health, Melbourne, Australia.

Perineuronal nets (PNNs) are thought to regulate neuronal plasticity and also provide protection to neurons -- primarily parvalbumin (PV+) neurons, known to be critical for normal cognitive functioning -- from damage. Thus, although the degradation of PNNs can increase plasticity and rescue cognitive impairment, such degradation might also render neurons vulnerable, with negative consequences. Here we designed an experiment to assess these two putative functions of PNNs, in the context of dietary-obesity induced memory impairment. It was predicted that enzymatic degradation of hippocampal PNNs with chondroitinase ABC would rescue memory ability when given following a memory-impairing high fat/ high sugar (HFHS) diet, but would exacerbate HFHS diet-induced memory impairments when given prior to the diet, due to damage from the diet to newly exposed neurons. The results confirmed this prediction: Recognition memory was restored in HFHS diet mice when PNNs were ablated following 4 weeks of HFHS diet consumption and then tested on the SLR task one week later. However, memory deficits in the SLR task were exacerbated when PNNs were removed prior to the 4-week HFHS diet consumption period. Furthermore, chemogenetic silencing of hippocampal PV+ neurons in PVCre mice that genetically express the inhibitory DREADD hM4Di demonstrated that memory performance in the SLR task is mediated by PV neuron activity, suggesting that the observed improvements and impairments of memory were due to facilitated and impaired functioning of PV neurons specifically. These studies provide evidence, in the same experimental setting, for the dual role of PNNs in plasticity and protection, and provide further evidence for PNNs as a novel therapeutic target, but with the caveat that both beneficial and detrimental effects of PNN manipulations can be obtained depending on the timing of PNN manipulation.

Funding Acknowledgement: Canada First Research Excellence Fund BrainsCAN, Natural Sciences and Engineering Research Council, Australian Research Council

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Speaker

Amy Reichelt Western University

A website for prevention of Alzheimer's disease.

A Website for Prevention of Alzheimer's DiseaseReid, Larry; Walf, AliciaRensselaer Polytechnic Institute An inspection of the vast literature on late onset Alzheimer's Disease (Alz) can be summarized rather easily. Alz is terrible eventually robbing citizens of their mind and ultimately their lives. There is no cure for Alz once its beginnings are established. A few drugs provide some temporary benefit, but do not stop the insidious progression of Alz. An initial sign of Alz is reduction in cognitive skills that becomes progressively more serious over time (for some, it may take years to progress toward dementia). Women are affected more than men. Aging is a risk for developing Alz, but about half of citizens of prosperous nations will live beyond their 60th birthday without developing Alz. A goodly proportion of those living in the 8th and 9th decades of life are without Alz and retain most of their cognitive skills. Epideminological research has identified a number of risk-factors associated with development of Alz. Some names of risks subsume other names. For example, a sedentary life-style summarizes risks of a poor diet and nutrition and inadequate physical exercise. The physiology associated with poor nutrition can be corrected by better nutrition and better nutrition is a trainable habit. There are well-establish programs for improving exercise. Chronic insomnia is a risk-factor for developing Alz because poor sleep hinders the clearance of proteins form interstitial fluid of the brain (a problem thought to kill neurons, hence a cause of Alz). We have cognitive behavioral treatments that can correct poor diets, inadequate exercise, and insomnia and in so doing correct the physiology of the brain and be preventive steps toward no Alz being developed. In addition to the 3 risk-factors just mentioned we have identified the following risks: insomnia and hyposmia, polypharmacy, air pollution, stress, and insufficient cognitive stimulation. We developed a website to address each risk. We refer citizens to successful commercial programs addressing a risk (e.g. WeightWatchers) and advise citizens with a risk on how to overcome the risk. In brief, we have approached the issue of Alz by engaging in biologically and sociologically informed cognitive behavioral technologies in the service of nudging older citizens to do activities that will likely slow or even prevent the development of Alz.

Speaker

Larry Reid Professor of Psychology and Neuroscience, Rensselaer Polytechnic Institute

Interactive Effects of Gender and Exposure to Western Diet on Shuttling Behavior During Avoidance and Pavlovian Instrumental Transfer Tasks in Rats

Pavlovian and avoidance conditioning commonly utilize rodents to model disorders of fear and anxiety in humans. However, an understanding of how these fundamental learning paradigms might differ on the basis of gender is only just starting to coalesce. The current project adds to this by examining how exposure to a high-fat, high-sugar (HFHS) diet influences learning and performance on a variety of aversively motivated learning tasks across male and female rats. HFHS food (also known as the Western diet) has been reported to increase anxiety and impair Pavlovian fear extinction, but whether similar effects might be observed in avoidance learning is unknown. In this study three diet-schemes were used to simulate differing degrees of exposure to a Western diet in humans. These included constant access to standard chow as a control, daily 2-hour access to HFHS pellets starting at post-natal day 28, and constant access to HFHS beginning prenatally via dams' milk. Two different groups of subjects underwent training on either a signaled avoidance task or an aversive Pavlovian-instrumental transfer (PIT) task using unsignaled Sidman avoidance. Constant access to HFHS food but not limited daily access to HFHS reduced two-way shuttle responding during signaled avoidance acquisition and extinction. Females in the daily 2-hour HFHS group extinguished faster than males in the same group. While diet did not impact Sidman avoidance or PIT, there was a gender effect such that females generally shuttled more than males during these tasks. Our results indicate that a Western diet may selectively interfere with regulation of negative affect in a gender specific manner. These findings suggest that risk factors which alter classical fear conditioning and extinction may also affect avoidance behaviors; therefore, further research using avoidance paradigms should be conducted to further grasp the development and function of fear-motivated learning and how it may be influenced by diet and gender.This research was partly funded by University of Evansville's Student Government Association Academic Fund Board

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Speaker

Piper Rennerfeldt

The choice to seek social interaction versus food differs with age and between Wistar rats and C57BL/6J mice

The choice to seek social interaction versus food differs with age and between Wistar rats and C57BL/6J mice.CJ Reppucci 1, LA Brown 1, AQ Chambers 1, & AH Veenema. 1 Neurosci. Program; Dept. of Psychology, Michigan State University, East Lansing, MI 48824. Many laboratory studies have focused on better understanding the peripheral and central systems that regulate the expression of a single behavior or the expression of a suite of behaviors associated with a single motivational state. In daily life, however, an individual can be simultaneously experiencing multiple motivational states with multiple choices of how to act. Here we characterized the Social versus Food Preference Test, a behavioral paradigm designed to investigate the competition between the choice to seek social interaction versus the choice to seek food. To determine how this competition is modulated by internal cues, we altered the motivational states of subjects by exposing them to acute social isolation and/or acute food deprivation, and examined whether the effects of these manipulations were similar between the sexes (males, females), stable across the lifespan (adolescents, adults), and comparable between commonly used laboratory rodent models (Wistar rats, C57BL/6J mice). In all cases, subjects were placed in a 3-chamber apparatus where a social stimulus (unfamiliar age-, sex-, and species-matched conspecific) and a food stimulus (standard lab chow) were corralled on opposite sides, and preference was determined by the relative amount of time subjects spent investigating each stimulus. We found that behavior in this test was similar between the sexes and unaffected by social isolation, but highly influenced by food deprivation (i.e., biased preference more

towards the food stimulus) and that this effect size was larger in adolescents than adults. Most strikingly, we observed a robust baseline difference in stimulus investigation patterns between Wistar rats and C57BL/6J mice: Wistar rats spent, on average, 258% more time investigating the social stimulus than C57BL/6J mice, and C57BL/6J mice spent, on average, 241% more time investigating the food stimulus than Wistar rats. Together, these experiments confirm that the Social versus Food Preference Test is suitable for future interrogations of the peripheral and central systems that can coordinate the choice to seek social interaction versus the choice to seek food. Research supported by NIMH R01MH102456 and NSF IOS 1735934 to AHV.

Speaker

Christina Reppucci Postdoctoral Researcher, Michigan State University

Analysis of gender diversity in IBNS speakers, chairs, and awardees from 2015-2019

Analysis of gender diversity in IBNS speakers, chairs, and awardees from 2015-2019. Millie Rincón-Cortés, Tiffany S. Donaldson, Gregory Carr, Susan Sangha, Stephen Kent, Jared Young, Marianne Van Wagner, Amanda C. Kentner, and Debra Bangasser.The International Behavioral Neuroscience Society (IBNS) promotes research and education in behavioral neuroscience across the globe. The Ethics & Diversity (E & D) Committee was created in 2019 to oversee our commitment to diversity, equity and inclusion across all levels of our Society. One goal of the E & D Committee is to collect and analyze historical data on gender diversity within the IBNS in regard to invited speakers, including keynote, presidential lecture and symposium speakers, conference chairs, as well as award recipients. Here, we present a retrospective analysis on gender diversity in the aforementioned speaker categories spanning the past 5 years (2015-2019). For the awards analysis, the categories of Travel Awards, Best Poster Awards, Early Career Awards, Fellows and Outstanding Achievement Awards were included. We counted the total number of people who have been a speaker (all roles, as described above), a chairperson, or an awardee based on the conference programs for these years. Of the total keynote/presidential lecture speakers, 61% were men and 39% were women. In the years 2015-2019, 55% of symposium chairs were men, and 45% were women. Similar numbers were found for speakers during this period, 54% were men and 46% were women. During 2015-2019, a total of 108 travel awards were given: 43% of recipients were men and 57% were women. From 2015-2019, there were a total of 18 poster awards: 44% of recipients were male and 56% were female. During this same period, there were 5 Early Career Achievement Awards, and 40% of recipients were male and 60% were women. From 2016-2019, 12 IBNS members have been elected as fellows: 50% were men and 50% were women. Four Outstanding Achievement Awards were awarded from 2016-2019, 75% were men and 25% were women. The gender parity among individuals selected as speakers, chairs and awardees is encouraging, although significant divergences from parity at the level of the Outstanding Achievement Award were detected. These data will be presented in detail, including a yearly breakdown, at the Annual Meeting and represent one of the initial steps of an ongoing effort to monitor the performance of the IBNS on our goal of having a diverse and inclusive society.

Speaker

Millie Rincón-Cortés Research Assistant Professor, University of Pittsburgh

Corticotropin-releasing factor receptor type 1 regulates context-cocaine memory reconsolidation in the basolateral amygdala

Corticotropin-releasing factor receptor type 1 regulates context-cocaine memory reconsolidation in the basolateral amygdalaRitchie, Jobe; Walters, Jennifer; Galliou, Justine; Grogan, Shayna; Fuchs, Rita.Department of Integrative Physiology and Neuroscience, College of Veterinary Medicine, Washington State University, Pullman, WA, USAExposure to drug-associated environmental stimuli results in the retrieval of drug-associated associative memories and can elicit drug craving and relapse in cocaine users.

Upon retrieval, drug-associated memories become destabilized and require memory reconsolidation to maintain their strength over time. Accordingly, interference with memory reconsolidation may promote drug abstinence. The basolateral amygdala (BLA) is a critical brain region for cocaine-memory reconsolidation. Corticotropin-releasing factor receptor type 1 (CRFR1) is densely expressed in the BLA, and CRFR1 stimulation activates signaling cascades that are necessary for memory reconsolidation. Hence, we tested the hypothesis that CRFR1 stimulation in the BLA is requisite for cocaine-memory reconsolidation. Using an instrumental rat model of drug relapse, male and female rats were trained to self-administer intravenous cocaine infusions in a distinct environmental context (10 days) followed by extinction training in a different context (7 days). Next, rats were re-exposed to the cocaine-paired context for 15 min, to reactivate cocaine memories, and then received bilateral vehicle, CRF (30 or 500 ng/hemisphere), or the CRFR1 antagonist, antalarmin (500 ng/hemisphere) infusions into the BLA. Drug context-induced cocaine seeking, an index of cocaine-memory strength, was assessed three days later. Females exhibited more active-lever responding than males during cocaine self-administration and extinction training; however, the effects of the CRFR1 manipulations on cocaine-memory reconsolidation were not sex specific. Antalarmin administration immediately after memory reactivation (i.e., during memory reconsolidation), but not six hours later (i.e., after memory reconsolidation), attenuated drug context-induced cocaine seeking at test relative to vehicle. CRF had similar effects on behavior, likely due to rapid CRFR1 desensitization/internalization. Thus, CRFR1 signaling in the BLA facilitates cocaine-memory strength during reconsolidation and may be a suitable target for future anti-relapse treatment strategies.This research was funded by NIDA R01 DA025646 (RF)

Speaker

Jobe Ritchie PhD Student, Washington State University

Disentangling motor deficits from anxiety-like behaviour in zebrafish and mouse models of the neurodegenerative disease Machado Joseph Disease

Disentangling motor deficits from anxiety-like behaviour in zebrafish and mouse models of the neurodegenerative disease Machado Joseph Disease. Katherine J Robinson, Maxinne Watchon, Angela S Laird, Centre for Motor Neuron Disease Research, Department of Biomedical Science, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW Australia Machado Joseph Disease (MJD), also known as spinocerebellar ataxia 3, is a fatal neurodegenerative disease resulting in progressive loss of motor coordination. MJD is caused by inheritance of an expanded trinucleotide repeat region within the ATXN3/MJD1 gene. MJD patients have also been reported to possess cognitive impairments, including deficits in verbal and visual memory, and anxiety. However, as MJD is an inherited disease, it is unknown if increased anxiety is a direct caused by the inherited genetic mutation or a consequence of disease anticipation. Within our studies, we have been using both zebrafish and mouse models of MJD, expressing mutant human ATXN3 with 84 and 138 polyQ repeats, respectively. We have previously reported significantly decreased swimming behaviour in response to darkness in six-day-old MJD zebrafish when compared to non-transgenic controls and zebrafish expressing unexpanded ATXN3 (containing 23 polyQ repeats, $p=0.002$). Similarly, our MJD mice exhibit impaired movement and balance, performing significantly worse in grip strength testing ($p<0.001$) and balance beam testing ($p<0.001$) when compared to wildtype littermate controls. Further analysis of movement within an open field revealed decreased movement in MJD mice ($p=0.004$) and a significant interaction effect (sex x genotype: $p=0.046$), whereby male MJD mice display increased thigmotaxis compared to MJD females ($p<0.05$). In contrast, MJD females display increased time in the centre compared to all groups. Interestingly, we have also found that adult MJD zebrafish spend more time swimming in the centre of the tank compared to non-transgenic controls, however quantification is required to confirm this effect. These observations were surprising, as anxiety-like behaviour has not previously been reported in animal models of MJD. However, the interpretation of anxiety-like behaviour is confounded by reduced movement. Future experiments will aim to further characterise MJD-dependent changes in anxiety-like behaviours in these animal models of MJD. In the MJD mice, we plan to examine behaviour in an elevated plus maze and novel object recognition to confirm the presence of cognitive phenotypes. These findings expand on previous data highlighting cognitive impairments and anxiety in MJD patients, providing insight into whether this disease phenotype is directly caused by mutation of the ATXN3/MJD1 gene or a consequence of disease anticipation. Funding Acknowledgement The authors would like to acknowledge funding from National Health and Medical Research Council of Australia (APP1146750), the MJD Foundation and Anindilyakwa Land Council, Australia, Macquarie University DVCR Research Support, The Swedish SCA Network, and The Snow Foundation.

Speaker

Katherine Robinson Postgraduate Student, Macquarie University

Sex-dependent noradrenergic modulation of premotor cortex during decision making

Sex-dependent noradrenergic modulation of premotor cortex during decision making. RodbergEllen denHartogCarol VazeyElena Department of Biology, University of Massachusetts Amherst, MA. Rodent premotor cortex (M2) integrates information from sensory and cognitive networks for decision related motor planning and movement initiation. M2 function is regulated by cortical inputs and ascending neuromodulators, including norepinephrine (NE) released from the locus coeruleus (LC). LC-NE has been shown to modulate the signal to noise ratio in target regions prior to decision execution, increasing the salience of relevant stimuli. To probe the role of NE on M2 function and cognitive performance, we used Î² adrenergic antagonist (propranolol) with extracellular electrophysiology in awake behaving rats (male and female) during a simple decision-making task, two-alternative forced choice (2AFC). Systemic propranolol altered task engagement while leaving completed trial accuracy intact. Impacts on performance were significantly greater in females than males but present in both sexes. Despite no change in accuracy, propranolol increased omitted trials and reaction and decision times in females. Analysis of single units from M2 (saline n=185, propranolol n=134) showed task related activity around important task epochs (cue onset, well exit, and lever press) with individual units preferentially driven by specific cues. Along with behavioral deficits, blocking Î² adrenergic signaling diminished task related excitation and inhibition in M2, greatly reducing the signal to noise ratio of population activity. Decision thresholds for cue processing within neural data were delayed prior to action completion. Overall, propranolol administration decreased the population of M2 units encoding task related information, decreased the magnitude of task related signals in remaining M2 units, and decreased the rate of information accumulation necessary to reach decision thresholds in M2 and behaviorally. Furthermore, we identified a sex bias where females are more impaired by disruptions of Î² noradrenergic signaling than males during simple decision making. Results from this study indicate that propranolol, by lowering Î² noradrenergic signaling, can impair focused decision-making and M2 task related neural activity and that sex-specific interactions in noradrenergic signaling influence cognitive function. Supported by National Institutes of Health awards R00MH104716 (EMV) and The University of Massachusetts Department of Biology.

Speaker

Ellen Rodberg Graduate Student, University of Massachusetts Amherst

The Consequences of a High-Fat Diet on Impulsive Decision-Making

The Consequences of a High-Fat Diet on Impulsive Decision-MakingKourtney Rumback, Anderson Fitch, Aubrey Deavours, Travis Smith, & Kimberly KirkpatrickKansas State UniversityProcessed saturated high-fat (HF) diets are implicated in negative health outcomes including impaired brain health and associated cognitive functioning. Recent findings in rodent models have shown that HF diets increase impulsive choices (i.e., suboptimal choices favoring a smaller-sooner, SS, reward over a larger-later, LL, reward). It is possible that these effects could be due to micronutrient deficiencies (i.e., vitamins and minerals) that often accompany HF diets. To assess this possibility, we compared two HF diets (relative to two low-fat, LF, control diets) on impulsive choices in rats. One HF diet came from supplemental vegetable shortening (along with normal chow) and the other diet came from commercial lard fortified with nutrients. Impulsive choices were evaluated using both grain pellets and fat pellets, to determine whether the reward type influenced choices. Food motivation was included as a secondary measure and evaluated motivation to work (i.e., lever press) for grain and fat pellets. Results showed that both HF diets increased impulsive choices when responding for both grain-pellets and HF-pellets. This demonstrated that processed/saturated HF diets increased impulsive choices even when controlling for micronutrients and that this effect does not depend on the type of food reward used to evaluate choices. Food motivation assessments showed that rats

maintained on a LF diet generally responded more for grain and fat pellets. HF diets have the potential to induce a vicious cycle in which impaired self-control results in escalation of HF consumption. Future research should focus on impulsive choices as a potential gateway to diet-induced obesity.This project was supported by NIH grants MH085739 and GM113109.

Speaker

Kourtney Rumback Undergraduate Research Assistant, Kansas State University

Contextual Fear Expression in Male and Female Rats

Contextual fear expression in male and female rats.Russo, Amanda; Voulo, Meagan; Parsons, Ryan. Stony Brook University, Psychology Department.Contextual fear conditioning (CFC) occurs when an individual learns to associate a specific context with an aversive stimulus such that they show a conditioned fear response to the context. Posttraumatic stress disorder (PTSD) is thought to be representative of persistence of conditioned fear. Although women are about twice as likely as men to be diagnosed with PTSD, the majority of work investigating conditioned fear has been conducted in males. Investigation of fear in rodents has shown that females show similar or lower levels of conditioned fear compared to males using freezing as a fear measure. However, work from our lab has found a response-specific sex difference in extinction of cued fear such that there is no difference between males and females when freezing is measured, but females show elevated fear following extinction compared to males when fear-potentiated startle (FPS) is measured. This suggests that FPS may be more sensitive in detecting elevated fear levels in female rats compared to freezing. Here, we asked whether there is also a response-specific sex difference in CFC. In Experiment 1, male and female rats were exposed to a CFC paradigm, where they received 3 shocks in Context A followed by a test in Context A during which percent time freezing was measured. We found that males froze more than females during a fear expression test. In Experiment 2, males and females were exposed to a contextual FPS procedure. Baseline startle response was measured before half the rats were trained in Context A with 3 foot-shocks, while the other half were exposed to Context A with no shock. Next, rats were presented with 20 noise bursts in Context A followed by 20 noise bursts in Context B. The percent change from startle at baseline to startle in both contexts was calculated. Preliminary results show no significant difference between males and females in contextual FPS. These data suggest that there is a response-specific sex difference in CFC such that females express a level of CFC similar to that of males when using an FPS measure, but not when using a freezing measure. Understanding sex differences in both cued and contextual conditioned fear will be crucial for understanding why women develop fear-related disorders more often than men and developing appropriate treatments for such disorders.

Speaker

Amanda Russo PhD Student, Stony Brook University

Dissecting the Role of BDNF and the Utility of Prophylactic Ketamine in a Ventral Hippocampal Fear Generalization Circuit

Dissecting the Role of BDNF and the Utility of Prophylactic Ketamine in a Ventral Hippocampal Fear Generalization Circuit. Ryan, James 1, Tse, Nathaniel 1, Jing, Deqiang 1, Lee, Francis. 1. Department of Psychiatry, Weill Cornell Medicine. Fear generalization is an adaptive mechanism conserved across species aimed at survival in the face of potentially life-threatening challenges. However, particularly traumatic situations can induce maladaptive overgeneralization to inappropriate stimuli, a behavior central to certain psychiatric disorders such as posttraumatic stress disorder (PTSD), via underlying neural and cellular mechanisms that remain largely unclear. Here, we address this question by first establishing a behavioral model of fear generalization induced by high-intensity (1.0mA) but not low-intensity (0.3mA) foot shocks during auditory fear conditioning in wildtype C57BL/6 mice. We then assess the role of brain-derived

neurotrophic factor (BDNF) in fear generalization by exposing mice with deficient activity-dependent BDNF secretion (Val66Met) to the fear generalization protocol as well as by prophylactic treatment with ketamine, a commonly-abused dissociative anesthetic that also exerts effects on synaptic plasticity and remodeling in part by a BDNF-dependent mechanism. Our results indicate that Val66Met mice exhibit fear generalization even when conditioned with the low-intensity 0.3mA foot shock, and further, that prophylactic ketamine treatment accelerates the extinction of generalized fear in wildtype mice but is less effective in BDNF Val66Met mice. To then parse out the neural circuits that mediate fear generalization, we assay immediate-early gene activity (c-Fos) and identify the ventral hippocampus CA1 (vCA1) as a region preferentially activated during fear generalization. We next use in vivo calcium imaging to measure population-level signaling activity in the vCA1 during fear and safety memory recall and find robust, tone-evoked and genotype-dependent changes in activity in mice conditioned with a high-intensity foot shock that is distinct from the signaling patterns seen in low-intensity foot shock-conditioned mice. Overall, our work demonstrates the significant role of the vCA1 and BDNF signaling in mediating generalized fear while also suggesting the potential therapeutic utility of prophylactic ketamine for the treatment of PTSD. Supported by NIDA T32DA039080 (JR) and NIH R01NS052819 (FL).

Speaker

James Ryan Graduate Student, Weill Cornell Medicine

Comparison of long-term effects of neonatal stressors on emotional behavior and hippocampal neuroimmune system in male and female rats

Comparison of long-term effects of neonatal stressors on emotional behavior and hippocampal neuroimmune system in male and female ratsSaavedra Luis Miguel1,2 HernÃ¡ndez Martha1, Madrigal Scarlette1, Ochoa Zarzosa Alejandra 2, Torner Luz 1 1Centro de InvestigaciÃ³n BiomÃ©dica de MichoacÃ¡n, Instituto Mexicano del Seguro Social, Morelia, MichoacÃ¡n, MÃ©xico. 2Centro Multidisciplinario de Estudios en BiotecnologÃa - FMVZ, Universidad Michoacana de San NicolÃ¡s de Hidalgo, TarÃmbaro, MichoacÃ¡n, MÃ©xico. Early life stress (ELS) increase the risk of suffering a psychiatric disease in adulthood. Severe neonatal infections also contribute to develop affective illness. These stressors trigger the immediate activation of the neuroimmune system. Here we compared the long-term effects of neonatal single or combined stress - immune challenges on emotional behavior and glial cell changes of the hippocampus. Male and female Sprague Dawley rats were used: 1) control + vehicle; 2) maternal separation (MS, 3h / day on postnatal days [PN] 1 to 14) + vehicle; 3) control + Lipopolysaccharide (LPS, 0.5 mg/ kg, PN14); 4) MS + LPS. Behavior was analyzed from PN120 in the males and from PN150 in diestrous females. Only LPS increased anxiety '"like behavior in male rats, whereas in females both challenges increased it. Regarding depressive '" like behavior, MS increased it in males, both LPS and MS increased it in females and combined stressors increased it in both sexes. Microglial cell density was unaffected in the hippocampal CA3 area of male rats, but was reduced by all stressors in the Hilus. In females, LPS decreased the microglial density in CA3 and Hilus. All stressors promoted microglial activation in CA3 and Hilus in males and females. In males, MS and LPS increased the astrocytic density of the Hilus, but only LPS increased it in CA3. MS prevented the increase of astrocytic density in response to LPS in both areas. In the females, only MS reduced the astrocytic population of the Hilus and CA3 areas. In conclusion, behavioral responses and glial cell changes to the challenges of early life depend on gender, suggesting a sexual dimorphism, and on the nature of the adverse event faced. (Fundings: CONACyT 243419 '" 2014 - FIS/IMSS/PROT/1386, and FIS/IMSS/PROT/PRIO/19/109).

Speaker

Luis Saavedra Comparison of long-term effects of neonatal stressors on emotional behavior and hippocampal neuroimmune system in male and female rats, Centro de Investigación Biomédica de Michoacán, Instituto Mexicano del Seguro Social

Sex differences in behavioral and metabolic phenotypes of diet-induced obese and diet-resistant rats

Sex differences in behavioral and metabolic phenotypes of diet-induced obese and diet-resistant rats. Elizabeth Sahagun, Dr. Kimberly P. Kinzig.Psychological Sciences, Purdue University, West Lafayette, Indiana.High-fat, high-sugar diets (HFHS) cause metabolic and neuroendocrine alterations linked to overweight and obesity. Although HFHS diets are known to contribute to overweight and obesity, less is understood about individuals that do not gain weight during HFHS access. Characterizing individual variation is crucial in understanding how HFHS diets impact obesity-resistant individuals that do not demonstrate drastic changes in body weight. These experiments focused on further understanding how HFHS impacts diet-resistant (DR) individuals differently than diet-induced obese (DIO), and to characterize DR and DIO phenotypes in females.In these experiments, male and female rats had access to HFHS for 12 weeks, during which caloric intake, body weight, and adiposity were measured. Glucose tolerance and corticosterone responses to a stressor were determined at the end of the experiment. Rats were phenotyped by tertiles according to body weight.We found that DIO males and females demonstrated typical hyperphagia and increases in adiposity in response to HFHS; effects were higher in females. DIO males had higher CH intake than DR, and female DIO had higher HFHS intake than DR. DR animals showed relatively mild hyperphagia and increases in adiposity compared to CTL. Hyperphagia in DIO and DR animals was only observed up until weeks 3-8, after which they consumed similar calories as CTL, indicating that body weight and adiposity remained high despite consuming fewer calories than at initial exposure. DIO females had altered glucose tolerance. DIO and DR males and females had opposite corticosterone responses. These data 1) provide knowledge to the metabolic and neuroendocrine changes effects of HFHS that may occur in normal weight individuals, 2) model the phenomenon reported in obese individuals that find it difficult to lose weight despite decreasing caloric intake, and 3) highlight that HFHS induces more deleterious neuroendocrine effects for females.

Speaker

Elizabeth Sahagun (she/her) Neuroscience PhD Candidate, Purdue University

The effects of maternal immune activation on mice lacking vesicular zinc

The effects of maternal immune activation on mice lacking vesicular zinc. Sandoval, Katy Celina 1, Niewinski, Nicole 1, Wong, Alison 1, Thackray, Sarah E 1, Dyck, Richard H 1. 1, University of Calgary. Maternal immune activation (MIA) during pregnancy has been associated with increased risk of neurodevelopmental disorders (NDDs) in offspring, such as schizophrenia (SZ) and autism spectrum disorders (ASD). Alterations to the maternal immune system are thought to lead to changes in the fetal environment and, thereby, contribute to the disruption of brain development. Other risk factors that contribute to NDDs are zinc deficiency in human subjects or by knocking out (KO) the zinc transporter 3 gene (ZnT3; slc30a3) in rodent models. ZnT3 is a protein that facilitates zinc packaging into vesicles within the axon terminals of glutamatergic neurons which is, consequently, released with glutamate into the synaptic cleft in an activity-dependent manner. We were interested in the effect of genetic deletion of zinc signaling (ZnT3 KO) combined with prenatal environmental stress (MIA) in male and female offspring relative to control groups. To study this effect, we induced MIA in pregnant female mice heterozygous for ZnT3 mid-gestation using the drug polyI:C which mimics a viral infection. We administered polyI:C (20mg/kg) or saline at embryonic day 12.5 as it is translational to the 2nd trimester of pregnancy in humans, a period in which MIA is thought to significantly contribute to NDDs. At postnatal day 9 (P9), we recorded ultrasonic vocalizations from all pups when isolated from the dam and nest and assessed their calls. Call duration usually reaches a peak between P7-P9 in mice. Starting at P60 (adult), male and female ZnT3 KO and wildtype mice were examined on a battery of behavioural tests commonly used to assess ASD- and SZ-like behaviour in rodents, including open field to assess anxiety, marble burying to assess repetitive behaviour, 3-chamber social test to assess social interaction, and pre-pulse inhibition to assess sensorimotor gating. Sex-specific differences were observed in response to MIA and/or lack of vesicular zinc: female offspring from polyI:C-treated mothers and female ZnT3 KO mice tend to be differentially affected by MIA compared to male offspring. By evaluating these behaviours, we will be able to determine the role of vesicular zinc in neurodevelopmental disorders, as well as the impact of loss of zinc interacting with the effects of MIA.

Speaker

Katy Celina Sandoval MSc Student, University of Calgary

Effects of maternal immune activation & environmental enrichment on estrogen receptor alpha numbers in the medial preoptic area & bed nucleus of the stria terminalis of postpartum female rats.

Effects of maternal immune activation & environmental enrichment on estrogen receptor alpha numbers in the medial preoptic area & bed nucleus of the stria terminalis of postpartum female rats. Shreya Sarmah 1, Matt Lukasik 2, Amanda C. Kentner 3, Anne T.M. Konkle 2,4,5. 1 Department of Biology, Faculty of Science, University of Ottawa, Ottawa, Ontario, Canada, 2 Interdisciplinary School of Health Sciences, University of Ottawa, Ottawa, Ontario, Canada, 3 School of Arts & Sciences, Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts, United States, 4 School of Psychology, University of Ottawa, Ottawa Ontario, Canada, 5 University of Ottawa Brain and Mind Research Institute, Ottawa, Ontario, Canada. Postpartum is a vulnerable time for mammals. Gestational perturbations are known to impact neurodevelopment but little is known about its effects on the maternal brain. Estrogen plays an important role in regulating maternal behavior via the activation of estrogen receptor alpha (ERa). The objective of this project was to evaluate the effects of maternal immune activation during pregnancy on the number of ERa in the BNST & MPOA, two brain areas involved in maternal behavior. We hypothesized that immune activation would reduce the number of ERa in the BNST & MPOA & an enriched environment would prevent these effects. Rat dams were randomly assigned to live in standard, socially or environmentally enriched housing. Dams received an injection of saline or lipopolysaccharide on gestational day 11. On postpartum day 22, brains were extracted, sectioned at 40 micrometers, & processed for immunohistochemistry with an antibody for the detection of ERa. Positive cell counts were performed with the software Image J. A factorial analysis of variance (ANOVA) was conducted to analyze the data. Maternal immune activation during pregnancy significantly reduced the number of ERa in the BNST of rats that lived in standard housing. This effect was not seen in those that lived in enriched housing. There is no notable effect of immune activation or housing on the number of ERa in the MPOA. These results speak to the consequences of maternal immune activation on the postpartum maternal brain & the need to further study the impact of environmental perturbations at this critical period of neuroplasticity. Funded by the Undergraduate Research Opportunity Program (UROP) scholarship.

Speaker

Shreya Sarmah Undergraduate Student, University of Ottawa

Child maltreatment and hypothalamic-pituitary-adrenal axis functioning: a systematic review and meta-analysis

Child maltreatment and hypothalamic-pituitary-adrenal axis functioning: A systematic review and meta-analysis Schaer, Selina1; Koenig, Julian1,2; Infurna, Maria 3; Muerner-Lavanchy, Ines 1; Schmidt, Stefanie 1; Kaess, Michael 1,2.1 University of Bern, Switzerland 2 Heidelberg University, Heidelberg, Germany3 University of Palermo, ItalyThe experience of child maltreatment (CM) is associated with the development of a wide range of mental health problems later in life. Chronic dysregulation of the hypothalamic-pituitary-adrenal axis (HPA axis) as a consequence of CM is discussed as one important mechanism in the development of mental disorders and has been extensively investigated. However, results from individual studies are mixed and inconclusive. In this meta-analysis, we aimed to quantify existing evidence on the effect of CM on cortisol metabolism. Case-control studies were identified by systematically searching several electronic databases. Using random-effects models (Hedges' g), separate meta-analyses were conducted on various measures of HPA axis activity (cortisol stress reactivity, circadian measures, pharmacological tests, hair and urinary cortisol) to provide a comprehensive assessment of the function of the HPA axis in individuals with CM compared to those without experiences of CM. Using meta-regression analyses, the effect of several moderators such as sex, age, current psychopathology and study quality remain to be examined. The systematic search returned 1858 articles of which k = 87 were included. Data extraction is not fully completed yet. Preliminary results across studies investigating the effect of CM on

cortisol stress reactivity yielded an average effect size of -0.32 (k = 28; N = 3674) with lower cortisol peak responses observed in participants with CM. Heterogeneity was high (I2 = 78%, p< 0.01), which suggests that other factors seem to be involved in modulating the effect of CM on the cortisol stress response. Interestingly, before being introduced to a specific stress task, participants with CM did not significantly differ from individuals without CM experiences with respect to baseline cortisol (Hedges' g = -0.13; k = 32; N = 3895). These preliminary results suggest a permanently changed regulation of cortisol release following exposure to a stressor in individuals with CM experience. Analyses of additional HPA axis outcome parameters will reveal whether this effect applies merely to stress reactivity, and are presented at the conference.

Speaker

Selina Schär University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Switzerland

How replicable is reactivation-dependent amnesia for contextual fear memories in rodents?

How replicable is reactivation-dependent amnesia for contextual fear memories in rodents?Schroyens, Natalie 1; Sigwald, Eric 1,2; Van Den Noortgate, Wim 1; Beckers, Tom 1; Luyten, Laura 11KU Leuven, Leuven, Belgium2INIMEC-CONICET-Universidad Nacional de CÃ³rdoba, CÃ³rdoba, ArgentinaResearch on memory reconsolidation has been booming in the last two decades, with numerous high-impact publications reporting promising amnestic interventions in rodents and humans. However, our own recently-published failed replication attempts of reactivation-dependent amnesia for fear memories in rats suggest that such amnestic effects are not always readily found and that they depend on subtle and possibly uncontrollable parameters, posing a challenge for clinical translation. The discrepancy between our observations and published studies in rodents suggests that the literature in this field might be biased. The aim of the current study was to gauge the presence of publication bias in a well-delineated part of the reconsolidation literature. We performed a systematic review of the literature on reactivation-dependent amnesia for contextual fear memories using commonly-used amnestic drugs in rodents and statistically investigated publication bias in this sample. To examine this further, and to get a better idea of the replicability of this effect, we are currently collecting unpublished data. We will present the preliminary results from our ongoing analyses and discuss their implications.Funded by a Consolidator Grant of the European Research Council (ERC, T. Beckers, grant number 648176) and Doctoral Fellowship of the Research Foundation, Flanders, Belgium (FWO, N. Schroyens, grant number 1114018N).

Speaker

Natalie Schroyens PhD Researcher - Psychology and Neuroscience, KU Leuven

Role of the nucleus reuniens in object memory consolidation in mice

Role of the nucleus reuniens in object memory consolidation in mice. Miranda R. Schwabe, Carnita M. Lincoln, Lisa R. Taxier, Karyn M. Frick. Department of Psychology, University of Wisconsin-Milwaukee, Milwaukee, WI 53211. Coordinated activity between the hippocampus and medial prefrontal cortex (mPFC) is required for memory encoding and retrieval. Our laboratory demonstrated that simultaneous subthreshold chemogenetic inactivation of the dorsal hippocampus (DH) and medial prefrontal cortex (mPFC) impairs the consolidation of object placement (OP) memory in female mice (Tuscher et al., 2018), suggesting that these two brain regions work in concert to promote memory consolidation. However, mechanisms through which these brain regions interact to promote memory consolidation remains poorly understood. A small cluster of cells in the midline thalamus known as the nucleus reuniens (RE) facilitates communication between the hippocampus and mPFC through bidirectional excitatory projections. Furthermore, recent work from other labs indicates that the RE is necessary for spatial working memory and fear extinction learning. The goal of this study was to determine whether activity in the RE is necessary for OP memory. Kappa-opioid receptor DREADD (KORD) virus activated by salvinorin B was used to

inactivate excitatory neurons in the RE. Mice infused with GFP virus or saline were used as controls. During training, mice were allowed to explore 2 identical objects placed near the corners of a large white box, and received a 10 mg/kg injection of salvinorin B either 10 minutes prior to training or immediately after training to target effects to the encoding and consolidation phases of memory, respectively. Testing was conducted 4h after training, a timepoint at which control mice remember the location of training objects. During testing, one object was moved to a different quadrant of the testing box. Activation of the KORD prior to or immediately after training blocked OP memory relative to chance and controls, supporting a key role for the RE in spatial memory consolidation. Current work is investigating the roles of specific projections among DH, mPFC, and RE. We include preliminary findings from retrograde labeling work using AAV-Cre-eGFP in a retrograde-specific serotype. Funding Acknowledgement: NIH Grant R01MH107886; Alzheimer's Association grant SAGA-17-419092, Sigma Xi Grant in Aid of Research to MS, UW-Milwaukee SURF Fellowship to CL.

Speaker

Miranda Schwabe Graduate Research Assistant, University of Wisconsin-Milwaukee

Cannabidiol (CBD) reduces the negative affective and somatic symptoms of opioid withdrawal.

Cannabidiol (CBD) reduces the negative affective and somatic symptoms of opioid withdrawal. Rhianne Scicluna1,2, Bianca Wilson1,2, Michael Bowen1,2. 1 The University of Sydney, 2 Lambert Initiative. The opioid epidemic is the deadliest drug crisis in American history, claiming more lives than guns or car accidents. Not only does opioid overdose kill more than 130 people a day in the USA, but this crisis is responsible for the loss of 3.4% of US GDP each year. The current situation can be directly linked to the over-prescription of opioids, usurping the brains reward system while creating tolerance and withdrawal, gating the transition to more dangerous opioids. Despite this, there is only one FDA approved non-opioid pharmacological treatment targeting acute withdrawal, and it is associated with a plethora of serious side effects. Fortunately, there is emerging epidemiological studies exploring the role of cannabis for opioid use disorder. It has been shown that when chronic pain populations are given access to cannabis, opioid use decreases by 40-60% and in states that have legalised medical cannabis, opioid mortality rates are lower. Further, a small amount of preclinical literature suggests that cannabidiol (CBD) might be effective for treating opioid use disorder. In the current research, we adapted and established murine models of naloxone-precipitated and spontaneous oxycodone withdrawal in mice to explore the effect of acute and chronic administration of CBD on oxycodone withdrawal. We found that acute administration of CBD following chronic oxycodone administration dose dependently inhibited some somatic symptoms of opioid withdrawal in mice, and caused pronounced inhibition of gastrointestinal symptoms. Further, we discovered that chronic co-administration of CBD and oxycodone dose dependently inhibited opioid withdrawal-induced jumps, an escape behaviour caused by withdrawal dysphoria. Currently, we are using immunohistochemistry techniques to examine the effects of CBD on neuronal activity in brain regions responsible for the somatic and negative affective symptoms of opioid withdrawal. This research has widespread implications.

Speaker

Rhianne Scicluna PhD Candidate & Casual Academic, The University of Sydney

Circadian modulation of neurons and astrocytes controls hippocampal plasticity and learning

Most animal species operate according to a 24-hour period set by the suprachiasmatic nucleus (SCN) of the hypothalamus. The rhythmic activity of the SCN is known to modulate hippocampal-dependent memory processes, but the molecular and cellular mechanisms that account for this effect remain largely unknown. Here, we show that there are cell-type specific structural and functional changes that occur with circadian

rhythmicity in neurons and astrocytes in hippocampal area CA1. Pyramidal neurons change the surface expression of NMDA receptors, whereas astrocytes change their proximity to synapses. Together, these phenomena alter glutamate clearance, receptor activation and integration of temporally clustered excitatory synaptic inputs, ultimately shaping hippocampal-dependent learning in vivo. We identify corticosterone as a key contributor to changes in synaptic strength. These findings identify important mechanisms through which neurons and astrocytes modify the molecular composition and structure of the synaptic environment, contribute to the local storage of information in the hippocampus and alter the temporal dynamics of cognitive processing.

Speaker

Annalisa Scimemi Associate Professor, State University of New York at Albany

Adult neurogenesis in the laboratory rat mediates forgetting of multiple types of memory

The formation and retention of hippocampus dependent memories is impacted by neurogenesis, a process that involves the production of new neurons in the dentate gyrus of the hippocampus. Recent studies demonstrate that increasing neurogenesis after memory formation induces forgetting of previously acquired memories. Neurogenesis-induced forgetting was originally demonstrated in mice, but a recent report suggests that the same effect may be absent in rats. Although a general species difference is possible, other potential explanations for these incongruent findings are that memories which are more strongly reinforced become resilient to forgetting or that perhaps only certain types of memories are affected. Here, we investigated whether neurogenesis-induced forgetting occurs in rats using several hippocampal dependent tasks including the Morris Water Task (MWT), contextual fear conditioning (CFC), and touchscreen paired associates learning (PAL). Neurogenesis was increased following training using voluntary exercise for 4 weeks before recall of the previous memory was assessed. We show that neurogenesis-induced forgetting is present in rats across behavioural tasks despite differences in complexity, aversive versus appetitive properties, and reliance on spatial, context, and object memories. In addition, we asked whether stronger memories are less susceptible to forgetting by varying the strength of training. However, even with a very strong training protocol we still observed enhanced forgetting related to increased neurogenesis. These results suggest that forgetting due to neurogenesis is a conserved mechanism that optimizes neural circuitry for the encoding of new memories.

Speaker

Gavin Scott Postdoctoral Associate, University of Calgary

The orbitofrontal cortex and the circuit mechanisms in the etiology and maintenance of diet induced obesity

The orbitofrontal cortex and the circuit mechanisms in the etiology and maintenance of diet induced obesity Seabrook, L., Kenney, T., Judge, A., Qiao, M., Borgland S.L.University of CalgaryThe lateral orbitofrontal cortex (lOFC) receives sensory information about food and integrates these signals with expected outcomes to guide future actions, and thus may play a key role in a distributed network of neural circuits that regulate feeding behaviour. Previously, we have demonstrated a novel role for the lOFC in the cognitive control of feeding behaviour in obesity. Obese mice have impairment of goal directed behaviour, such that mice continue to consume food regardless of satiety or sickness. Obesity is associated with a disinhibited lOFC, and chemogenetic reduction in lOFC GABAergic neurotransmission of lean mice induces obesity-like impairments in goal-directed behaviour. However, the time course of these events is unknown. We tested the hypothesis that short-term exposure to an obesogenic diet induces synaptic plasticity in the lOFC and drives over consumption. Similar to obese mice with 3 month high fat diet exposure, 7-day exposure to this diet is sufficient to disinhibit the lOFC. However, unlike obese mice, which exhibit hypertrophic astrocytes and a glial-dependent suppression of inhibitory synaptic transmission onto lOFC

pyramidal neurons, 7-day exposure to a high fat diet does not induce hypertrophic astrocytes. The microglial marker Iba-1 has increased expression in lOFC of obese, but not 7-day exposed mice. Furthermore, the astrocyte marker, S100 is upregulated in obese mice, but not after 7-day exposure. Finally, short term exposure to a high-fat diet does not alter goal-directed behaviour. Taken together, while disinhibition of the lOFC can occur early on in diet exposure, inflammatory mechanisms appear at later stages of diet exposure. Thus, future work will assess how inflammatory mechanisms in the lOFC during obesity influence goal directed behaviours.

Speaker

Lauren Seabrook University of Calgary

Alternative behavioral responses to fear conditioning are determined by genetic background.

Alternative behavioral responses to fear conditioning are determined by genetic background. L.R. Seemiller1, S.M. Mooney-Leber1, E. Henry1, A. Hess1, G. Peltz2, and T.J. Gould1. 1 Department of Biobehavioral Health, Penn State University, University Park, PA, USA. 2 Department of Anesthesiology, Perioperative, and Pain Medicine, Stanford University School of Medicine. Freezing is a classical measure of learning during fear conditioning. However, it is possible that expression of other behaviors may compete with this traditional measure of learning. Grooming and rearing are both complex behaviors frequently exhibited by mice during fear conditioning. Both behaviors have been shown to be stress-sensitive, with patterns of expression varying based on genetic background. Here, we aim to better understand how genetic background determines behavioral responses during fear conditioning. We examined how grooming and rearing frequencies varied during different stages of fear conditioning in male mice from eight inbred mouse strains (C57BL/6J, DBA/2J, FVB/NJ, SWR/J, BTBR T+ ltpr3Tf/J, SM/J, LP/J, 129S1/SvlmJ) with a wide range of freezing responses during fear conditioning. We used a time-sampling method to quantify grooming and rearing prior to footshock exposure (unconditioned stimulus) and during contextual and cued (CS '" conditioned stimulus) tests. Generally, strains that exhibited lower freezing expressed higher levels of rearing and grooming. We found significant main effects of strain on grooming and rearing frequencies across all (baseline, context, pre-CS, CS) conditioning stages. Main effects of strain were also found in all delta scores for both behaviors, calculated within individuals across baseline and context (context minus baseline) or pre-CS and CS (CS minus pre-CS) conditions, suggesting strain differences in conditioned responses. Using publicly available SNP data, we found that higher grooming frequencies across tests were associated with polymorphisms in Dab1, a gene that is related to both grooming and learning phenotypes. Together, these findings demonstrate that stress-sensitive rearing and grooming behaviors vary in expression during fear conditioning based on genetic background. Funding: U01DA04439902 (G.P.; T.J.G.), T32GM108563 (L.R.S.).

Speaker

Laurel Seemiller Graduate Student, The Pennsylvania State University

Hippocampal neurogenesis impacts delay-based decision making

Hippocampal neurogenesis impacts delay-based decision making Seib, Desiree R; Espinueva, Delane F; Princz-Lebel, Oren; Chahley, Erin; Stevenson, Jordann; Floresco, Stan B; Snyder, Jason S.Department of Psychology, University of British Columbia, Vancouver, Canada Depression is a complex disorder with disruptions in motivation, decision making and valuing future rewards. One brain region that has been implicated in the pathology of depression is the hippocampus. Interestingly, in humans it is the brain region that is capable of generating new neurons throughout life. To date, little work has thoroughly examined how a reduction in new neurons modulates the hippocampal network during behavior and which of the complex behavioral traits of depression are caused by reductions in neurogenesis. We examined the effect of reduced adult hippocampal neurogenesis on cost/benefit decision-making in a delay-discounting

operant task. Therefore, we used transgenic rats (hGFAP-TK), in which drug-treatment can deplete actively dividing neural progenitors in a time- and region-specific manner and consequently stop the production of new neurons. We then assessed delay-based decision-making in an operant task where rats can choose between a low/immediate reward and a high/delayed reward.In this model, the valuation of future rewards was selectively impaired in rats with reduced neurogenesis, i.e. animals were not willing to wait to receive a large food reward but rather chose a small immediate food reward, similar to what is observed in depression. Histological analysis from animals that had been trained on the task showed that first, animals without neurogenesis had a reduction in neuronal activity specifically in the ventral hippocampus, which is believed to be important for affective processing. Second, in wild type animals, neurons that were immature while animals were trained on the task showed changes in their morphology on the level of dendrites and mushroom spines compared to controls, indicating their involvement in assigning value to rewards. Third, neurons that were immature during task-acquisition were specifically recruited during task performance in the ventral dentate gyrus. These cellular data strengthen the behavioral results on the importance of adult neurogenesis for future rewards and highlight characteristics of neuronal integration and activation affected by behavior that might be disturbed in depression.Funding: CIHR, BBRF, DFG

Speaker

Desiree Seib Research Associate, University of British Columbia

Using environmental enrichment to minimize hypoxic-ischemic hippocampal atrophy in Long Evans rat pups

Using environmental enrichment to minimize hypoxic-ischemic hippocampal atrophy in Long Evans rat pupsJoanna Severino Perez1; Jeffrey La2, M.S.; Corey Calhoun3, B.A.; Brooke Plotkin3, B.A.; Briana Mason3, Ph.D.; LG Rollins4, Ph.D.; S. Tiffany Donaldson, Ph.D.1Department of Biology, 2Department of Physics, 3Developmental Brain Sciences, Department of Psychology, University of Massachusetts Boston, Boston, MA 021254Warren Alpert Medical School and The Miriam Hospital, Department of Behavioral and Social Sciences, School of Public Health, Brown University, Providence, RI 02906Hypoxia ischemia encephalopathy (HIE) is a condition in which there is diminished oxygen and blood flow to the neonate during the birthing process, resulting in neuronal dysfunction and sometimes, death. Individuals suffering from this injury will often go on to develop cerebral palsy, cognitive deficiencies, and mental illness. There is no existing cure, so investigations into treatment are warranted. After inducing the HI injury in Long Evans rat pups and assigning them to standard or environmentally enriched (closed nestbox) conditions, they were put through behavioral, neurodevelopmental, and morphological analyses. The brains were extracted, and coronal sections were taken to stain with Nissl. Finally, we took digital images of the microsections at 2.5x magnification using a Zeiss Axio Observer with motorized stage and stitching process, allowing us to take measurements of the bilateral hippocampus. Morphometric analysis of the bilateral hippocampus suggests that an enriched environment significantly impacts HI damage, reducing the difference in area induced by the injury between the left and right sides. The data suggests that the impacts of environmental enrichment are sexually dimorphic, with the improvements being more pronounced in male subjects. Closed nestbox individuals also exhibited a slight volumetric increase in comparison to their counterparts that were raised in standard housing conditions. These results suggest that environmental enrichment can potentially be implemented into treatment for hypoxia ischemia encephalopathy, minimizing the damage to the hippocampal area of the brain. This research is funded by the NIH

Speaker

Joanna Severino Perez

Sex-Related Differences in Animal Models for Autism Spectrum Disorder: A Systematic Review

Sex-related differences in animal models for autism spectrum disorder: a systematic review.

*Areeba Sharafuddin, Melika Babadi, Christina Y. Yin, and Florence I. Roullet. McMaster University, Hamilton, ON, Canada. *presenting*

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by social and communicative behavioural deficits. There are no physiological, anatomical and/or genetic hallmarks of ASD, however, one recurrent observation is that autism diagnoses are more prevalent in males than females, with a ratio varying between 3-5:1. Various theories, including the '˜extreme male brain theory' and the '˜female protective model', have been proposed to try and explain this unbalanced ratio, however the current body of research in ASD is male-dominant and little information is known about why females remain under-diagnosed. The aim of this study is to provide a quantitative and qualitative analysis of the current scientific literature describing sex-related differences in animal models of ASD. METHOD. Literature search for articles published from January 1, 2004 to February 2020 on PubMed and Medline was performed using keywords (animal model) AND (autism OR ASD) AND (sex or gender). Several automatic filtering systems were used. Articles were then screened at the '˜title and abstract' level using Rayyan software. Data extracted were organized into 4 behavioural categories relevant to the study of ASD: communication, social behaviour, locomotor/repetitive activity, anxiety, and one category brain imaging/biochemical/genetic tests. Within each category, several sub-categories were created according to the method employed. PRELIMINARY RESULTS. Of the 219 articles retrieved, after screening, 93 articles were included. Limiting this group of relevant papers to those published from 2017 to 2020, a total of 44 articles were included for the data extraction at the full-text level. Several animal models for ASD were used: genetic (e.g. Foxp1), idiopathic (e.g. EL), environmental (e.g. Maternal Immune Activation (MIA)), and a mix of genetic x environmental challenge (e.g. MIA x keto diet). We classified the sex-related differences reported into three types: Type 1) sex-related differences between males and females of the Control group, Type 2) sex-related differences between males and females of the Treatment group and Type 3) sex-related differences expressed as a significant statistical interaction of factors 'sex' by 'treatment'.

Speaker

Areeba Sharafuddin Undergraduate Student Researcher, St. Joseph's Healthcare Hamilton

Differential Effects of Two Types of Prolonged Restriction of Motor Activity on Behavior and Brain Ultra structure in Male Rats

Differential Effects of Two Types of Prolonged Restriction of Motor Activity on Behavior and Brain Ultrastructure in Male RatsIrina Sharikadze 1, Mzia Zhvania 1,21 School of Natural Science and Medicine, Ilia State University, Tbilisi, Georgia, 2 Department of Brain Ultrastructure and Nanoarchitecture, I. Beritashvili Center of Experimental Biomedicine, Tbilisi, GeorgiaRestraint stress has been reported to produce various changes, including behavioral and morphological alterations. The analysis of these changes is done in numerous studies, however little attention has been paid on the possibility that various types of restraint activities could produce differential effects. In this study, we clarify the effect of two types of prolonged restriction of motor activity on the process of learning, anxiety-like behavior, locomotor activity and ultrastructure/presynaptic architecture of central and lateral nuclei of amygdala, hippocampal CA1 area, caudate nucleus and prefrontal area in adult male Wistar rats. Two different types of restraint apparatuses and two groups of animals were used. The animals of first group were subjected to significant restraint of motor activity and second group were subjected to mild restriction of motor activity. ELISA revealed elevated level of blood plasma coricosterone only in rats of first group. Immediately after restriction of motor activity, behavioral and electron microscopic studies were done. Multi-branch maze, open field and elevated plus maze tests were used and statistical analysis of quantitative data was done. The data show that restraint stress affects learning and locomotion and induces anxiety-like behavior. Ultrastructural changes were detected in all regions, except prefrontal cortex. The most altered was amygdala, in lesser degree - the hippocampus and caudate nucleus: new part of neurons and synapses were irreversibly damaged. Mild restriction of motor activity produces the decrease of locomotion, anxiety-like behavior and moderate ultrastructural alterations - mostly in caudate nucleus, lesser in amygdala. Quantitative electron microscopic analysis revealed that both models induce changes in the number of synapses, number of synaptic vesicles, ratio of asymmetric and symmetric synapses, and ratio of synapses on spines/thin dendrites and dendritic shafts. Overall, the data suggest that the cause of main part of alterations provoked by chronic motor deficit is stress, which often accompanies this condition.

Speaker

Irine Sharikadze PhD Student, Ilia State University

Chronic predation stress and low-level inflammation alters cognition and synaptosomal respiration in C57Bl/6 mice

Chronic predation stress and low-level inflammation alters cognition and synaptosomal respiration in C57Bl/6 mice. Gladys Shaw 1, Molly Hyer 1, Imogen Targett 1, Kimaya Council 1, Samya Dyer 1, Susie Turkson 1, Chloe Burns 1, Gretchen Neigh 1. 1 Department of Anatomy and Neurobiology, Virginia Commonwealth University, Richmond, VA. Background: Chronic stress and increased systemic inflammation may heighten risk of neurodegenerative disorders. This project aims to assess the influence of chronic stress and chronic inflammation on synaptosomal metabolism and related changes in cognitive ability. Methods: 63 male and female C57Bl/6 mice were subject to chronic repeated predation stress (male n=15; female n=16) or daily handling (male n=16; female n=16) for 15 days during adolescence and again during early adulthood. Mice were then subject to 8 weeks of chronic lipopolysaccharide (LPS) or saline injections to induce low-level peripheral inflammation. Open field testing assessed anxiety-like behavior. Barnes Maze was used to assess cognition. Whole brain synaptosomes were isolated and assessed for mitochondrial respiratory capacity. Both transcript and protein levels of ROMO-1 and various inflammatory markers were also acquired. Results: Open field data display a main effect of stress. Stress and inflammation decreased synaptosomal respiration in both sexes, yet inflammation alone increased synaptosomal respiration in females with no stress history. There were no significant changes in transcript levels of ROMO-1 in any group, yet protein assessment displayed a main effect of treatment in males. Conclusion: Chronic stress induces long-lasting anxiety-like behavior which is attenuated by chronic inflammation in both male and female mice with a history of stress with marginal alterations in cognitive behavior. The changes in synaptosomal respiration suggest that sex, stress, and inflammation interact to create a unique metabolic profile. These data highlight how sex, stress history, and inflammation interact, shaping individualized behavioral patterns driven by mitochondrial bioenergetics. Funding Acknowledgement: Microscopy was performed at the VCU Microscopy Facility, supported, in part, by funding from NIH-NCI Cancer Center Support Grant P30 CA016059. Primary research funded by Alzheimer's Research Supplement to NINR R014886 (GN), IRACDA Fellowship K12GM093857 (MH), and IMSD Fellowship 5R25GM090084-08 (GS).

Speaker

Gladys Shaw PhD Candidate, Virginia Commonwealth University

Diet-induced deficits in goal-directed control are rescued by agonism of Group II metabotropic glutamate receptors in the dorsomedial striatum

Diet-induced deficits in goal-directed control are rescued by agonism of Group II metabotropic glutamate receptors in the dorsomedial striatum.
Shipman, Megan L.; Corbit, Laura H.University of Toronto
Generally, operant behaviour begins as goal-directed and sensitive to reinforcer devaluation and transitions across training to habitual and insensitive to outcome devaluation. However, obesogenic diet or drugs of abuse can disrupt this, resulting in insensitivity to devaluation while controls remain goal-directed. This occurs even though the drug/diet is given and discontinued prior to training, and when responding is trained for different food reinforcers, indicating that this manipulation promotes lasting neural changes. However, the mechanisms for this are unknown. It has been well-established that the dorsomedial striatum (DMS) mediates goal-directed responding while the dorsolateral striatum (DLS) mediates habit, and these areas are part of parallel and interacting circuits. Recent work has shown that cocaine-induced habitual responding may be due to increased excitation of the DMS rather than the DLS, indicating a disruption of goal-directed regions rather than a facilitation of habit regions. Here, we examined whether obesogenic

diet-induced behavioural deficits could be ameliorated by mGluRII agonism specifically within the DMS, indicating that the behavioural deficit was due to DMS dysfunction. First, we provided rats continuous access to sweetened condensed milk (SCM) for 7 weeks. Following training, control rats showed sensitivity to reinforcer devaluation while SCM rats were insensitive to reinforcer devaluation. In Experiment 1, we showed that an intraperitoneal injection of a mGluRII agonist (LY379268) results in goal-directed responding in SCM rats. In Experiment 2, we infused the mGluRII agonist directly into the DMS. Preliminary results indicate that this too may restore diet-induced disruption of goal-directed responding.This work was supported by the Canadian Institutes of Health Research [funding reference number 401526].

Speaker

Megan Shipman postdoctoral fellow, University of Toronto

Reduced Resting-State Heart Rate Variability is a Potential Mediator between Early Life Maltreatment and Psychopathology: Meta-Analytic and Exploratory Evidence

Reduced Resting-State Heart Rate Variability is a Potential Mediator between Early Life Maltreatment and Psychopathology: Meta-Analytic and Exploratory Evidence. Christine Sigrist 1, Ines MÃ¼rner-Lavanchy 1, Stephanie K.V. Peschel 2, Stefanie J. Schmidt 3, Michael Kaess 1, 4, Julian Koenig 1, 5. 1 University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, 2 Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, 3 Department of Clinical Psychology and Psychotherapy, University of Bern, 4 Section for Translational Child and Adolescent Psychiatry, Department of Child and Adolescent Psychiatry, Centre for Psychosocial Medicine, University of Heidelberg, 5 Section for Experimental Child and Adolescent Psychiatry, Department of Child and Adolescent Psychiatry, Centre for Psychosocial Medicine, University of Heidelberg. Vagally-mediated resting-state heart rate variability (vmHRV) is regarded as a non-invasive biomarker reflecting fast parasympathetic modulation of autonomic control of the heart. Reductions in vmHRV, potentially reflecting critical aberrations in stress regulatory capacities, have been found to precede psychopathology onset. Experiences of early life maltreatment (ELM) are consistently and strongly associated with the emergence of psychopathology later in life. In a systematic review and meta-analysis, we aimed to clarify the direct link between ELM and vmHRV, given that existing studies reported inconsistent results and have previously not been systematically reviewed. We assumed that vmHRV would be reduced in individuals with ELM compared to individuals without such experiences, that the severity of ELM would correlate inversely with vmHRV, and that there are potential moderators of these relationships. In accordance with the current literature, ELM was defined as chronic or severe experiences of threat and/or deprivation that represent a deviation from the expectable environment of an average child and require psychological or neurobiological adaptation. Time- or frequency-domain measures of vmHRV were included. We conducted a systematic search and screened for studies reporting group comparisons and/or correlations. By quantitative synthesis of 32 eligible studies using random-effects models, we found no evidence for a relationship between ELM and vmHRV in principal. Conducting meta-regression analyses, however, we found the relationship between ELM and vmHRV to vary as a function of both age and presence of psychopathology. Studies including older-aged samples reported significantly greater reductions in vmHRV in association with ELM exposure severity than studies based on younger samples. In samples drawn from clinical populations where most individuals reported psychopathology, as compared to general population samples, we found vmHRV to be more strongly reduced in the group that had experienced ELM. While these moderator analyses were exploratory in nature, our results emphasize the need for future longitudinal studies examining the causal link between ELM and vmHRV.

Speaker

Christine Sigrist Doctoral Student, University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Switzerland

Effects of intravenous oxycodone self-administration and contextual renewal of oxycodone-seeking behavior on ultrasonic vocalizations (USVs) in rats

Effects of intravenous oxycodone self-administration and contextual renewal of oxycodone-seeking behavior on ultrasonic vocalizations (USVs) in rats. Steven Simmons1, Raena Greenbaum1, William Haury1, Haley Phillips1, Paula Muñoz Rodríguez2, Hannah Deutsch1, Amelia Eisch1, 3. 1 Children's Hospital of Philadelphia, 2 University of Puerto Rico, 3 University of Pennsylvania. Opioid abuse is a pervasive public health problem that devastates the wellbeing of individuals, families, and communities. Self-reports suggest the prescription opioid oxycodone possesses "unparalleled addictive potential". Measuring this subjective likability of oxycodone in animals is important to better evaluate oxycodone's abuse potential. To meet this need, we recorded ultrasonic vocalizations (USVs) — interpreted to reflect positive and negative affective states based on emission frequency — in rats trained to self-administer oxycodone. Adult male Long-Evans rats (N=12) trained (3h/d, 6d/wk, 18d; "acquisition") to bar press for 3-s infusions of oxycodone (days 1-12: 0.10 mg/kg/inf; days 13 to 18: 0.05 mg/kg/inf). A subset of rats proceeded to extinguish bar pressing in an alternate context (3h/d, 6d/wk, 12d; "extinction"). For the reinstatement test, rats were returned either to the oxycodone-paired context (ABA) or the extinction context (ABB). USVs were recorded during the entire self-administration session, and for 5 min prior to self-administration, on days 1, 7, and 13 of acquisition as well as during reinstatement. Results show that, during acquisition, rats emit more 50-kHz USVs during pre- and post-lever periods on days 7 vs. day 1 (and more pre-lever 50-kHz USVs on day 13 vs. day 1). A within-session analysis shows that 50-kHz USVs drop to near-zero levels after ~15 min of self-administration on all recorded days despite continued oxycodone self-administration. During reinstatement, ABA rats both pressed more and emitted greater 50-kHz USVs vs. ABB rats. These data suggest that a positive anticipatory (pre-drug) response develops as rats learn that contextual stimuli predict the opportunity to self-administer oxycodone. Surprisingly, USVs during reinstatement suggest that returning to an opioid-paired context elicits a positive (albeit transient) subjective state. Finally, correlational analyses from this study show the relationships between USVs and drug-taking and -seeking behaviors are intriguingly mixed and warrant additional study. Future studies will be designed to better understand the neurocircuitry underlying the maintenance and retrieval of contextual memories shown to imbue physical environments with salience and relapse-driving properties. Funding: T32-NS007413 (NINDS; SJS/AJE), Development Funds (CHOP Dept. of Anesthesiology; AJE).

Speaker

Steven Simmons Postdoctoral Researcher, Children's Hospital of Philadelphia Research Institute

N-ACETYLCYSTEINE REDUCES COMPULSIVE-LIKE BEHAVIOUR TOWARDS HIGH-FAT HIGH-SUGAR FOOD IN DIET-INDUCED OBESE RATS

N-Acetylcysteine reduces compulsive-like behaviour towards high-fat high-sugar food in diet-induced obese rats.

Sketriene D, Battista DC, Lawrence AJ, Brown RM.

The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

Pathological overeating displayed by obese individuals shares similarities with compulsive drug taking behaviour observed in drug-addicted subjects. This raises the possibility that drug addiction treatments may show utility in the treatment of compulsive overeating. N-Acetylcysteine (NAC) is a cysteine pro-drug which has experienced some success in clinical trials for reducing cocaine, marijuana and cigarette use, as well as compulsive behaviours such as gambling and trichotillomania. We assessed the impact of NAC on addiction-like behaviour towards highly palatable food in a rat model of diet-induced obesity. Diet-induced obesity-prone (DIO) and resistant (DR) rats were subjected to an operant conditioning paradigm whereby rats were allowed to lever press for high-fat high-sugar food pellets (S+). This alternated with periods of signalled reward unavailability (S-). DIO animals responded more during S+ periods and earned more food pellets. Vehicle-treated DIO rats increased their lever presses over the 2 weeks self-administration period, but this escalation was absent in NAC-treated DIO rats. Compared to DR rats, DIO rats responded significantly more during S- periods, indicative of compulsive-like food-seeking. The persistent S- responding in DIO rats was ameliorated by daily injections of NAC (100 mg/kg, i.p.) administered 2 h prior to the operant session for 14 days. By the end of the treatment period, there was no significant difference in S- responding between NAC-treated DIO rats and DR rats, whereas S- responding in vehicle-treated DIO rats remained significantly higher ($p<0.05$). These findings suggest that NAC modifies aspects of food-

seeking behaviour in DIO rats and supports the potential use of this compound in compulsive overeating and related forms of obesity.

Speaker

Diana Sketriene PhD candidate , The Florey Institute

Neuronal ensembles activated by acquisition of cocaine-seeking preferentially project to the nucleus accumbens shell.

Neuronal ensembles activated by acquisition of cocaine-seeking preferentially project to the nucleus accumbens shell.Authors: Bo Sortman 1, Christina Gobin 1, Richard Quintana-Feliciones 1,2, Samantha Rakela 1, Namratha Tarigopula 1 , Brandon Warren 1.1 University of Florida, College of Pharmacy, Department of Pharmacodynamics.2 Mount Sinai, Icahn School of Medicine.We have previously shown that distinct Fos-expressing neuronal ensembles in the Ventral Medial Prefrontal Cortex (vmPFC) mediate both self-administration and extinction of cocaine seeking behavior. These neuronal ensembles drive cocaine seeking via projections to the nucleus accumbens core. However, it is not yet clear when this anatomical separation of function emerges. Here, we test the hypothesis that neuronal ensembles emerge during initial acquisition of cocaine-seeking behavior and are selected based on their projections to subregions of the nucleus accumbens. To test this hypothesis, we injected fluorescently labeled cholera toxin subunit B (CTb) into the Nucleus Accumbens Core (NAcC) and Shell (NAcSh). We then allowed rats to lever press for infusions of cocaine (0.75 mg/kg/infusion) for between 1-5 days, until the rats self-segregated into 'œlearners' and 'œnon-learners' based on their inclination to lever press for cocaine. Twenty-four hours after the last acquisition session, we placed rats into the operant chamber under non-reinforced conditions to test their recall of cocaine-seeking. We reasoned that during this recall session, neuronal ensembles would be reactivated and would induce Fos expression. We sacrificed the rats 90 min after the start of the recall session and measured co-labeling of Fos and CTb. We found that neuronal ensembles activated during acquisition of cocaine-seeking preferentially project to NAcSh. This finding suggests that neuronal ensembles activated during recall of acquisition of cocaine seeking may drive cocaine-seeking through projections to the NAcSh.NARSAD Young investigator grant; R00DA042102

Speaker

Bo Sortman University of Florida

Repurposing metformin for reducing cue-induced reinstatement for cocaine.

Repurposing metformin for reducing cue-induced reinstatement for cocaine.Authors: Chan, Amy; Willard, Alexis; Sciaccotta, Allegra; Mulloy, Sarah; Spencer, Sade1 University of Minnesota, Minneapolis, MN. Drug craving is a central characteristic of addiction that can be elicited by re-exposure to drug-associated cues. Here we tested the effectiveness of metformin, an FDA-approved type II diabetes medication, for reducing cue-induced reinstatement in a rat model of cocaine seeking. Among other mechanisms, metformin is an indirect activator of adenosine monophosphate activated protein kinase (AMPK). Previously it has been shown that activating AMPK in the nucleus accumbens core (NAcore) with an allosteric activator AICAR decreases cue-induced reinstatement in a rat model of cocaine seeking; however, the translational potential of AICAR is limited because it fails to readily cross the blood-brain barrier. Initial studies were undertaken to determine if metformin, which can readily access the central nervous system, is likewise able to inhibit reinstatement responding when microinjected in NAcore. Male and female Sprague-Dawley rats were trained to self-administer intravenous cocaine (0.4 mg/0.1 ml/infusion) and then were tested for cue-elicited cocaine seeking following extinction training. Using a within-subjects design rats were microinjected with 0.9% sterile saline vehicle or (125 Âµg/0.5 Âµl) metformin and then subjected to a 2-hr test for cue-elicited cocaine seeking. Separate experiments examined the effects of metformin on cue-elicited sucrose seeking in sucrose-trained rats. We found that intracranial metformin in the NAcore was effective at reducing cue-

induced reinstatement for cocaine in both male and female rats. Metformin also reduced cue-induced sucrose seeking in female rats (experiments in male subjects are in progress). These data provide novel, evidence that acute intra-NAcore metformin pretreatment inhibits cued cocaine seeking in a rat model of relapse, but this effect may not be specific to drugs of abuse. We hypothesize that activating AMPK may be the mechanism of action through which metformin exerts its anti-craving effects, and experiments are ongoing to validate this mechanism given that metformin targets multiple signaling pathways. The next step will be to extend these studies to examine systemic administration of metformin, and if effective, determine whether a similar or distinctive mechanism of action is engaged. This work was supported by NIH grant DA041462 and start-up funds from the University of Minnesota.

Speaker

Sade Spencer Assistant Professor, University of Minnesota, Minneapolis, MN

Peer-rearing is only beneficial if you have an engaging partner

Peer-rearing is only beneficial if you have an engaging partnerR. A. Stark, M. Szabo, & S. M. PellisUniversity of Lethbridge, Alberta, CanadaRough-and-tumble play is the most common form of play reported in young animals. Adult male Long-Evans Hooded (LE) rats, a highly playful strain, that had been reared as juveniles with a partner of a less playful strain, Fischer-344 (F-344), were socially deficient. Social competence was assessed in the stranger paradigm, in which two unfamiliar rats are placed together in a neutral arena, where they will play to assess their dominance relationship, without escalating to serious fighting. Long-Evans rats reared with F-344 partners were more likely to escalate these encounters. We hypothesized that this reduced social ability was due to impoverished play experiences as juveniles. Therefore, we assessed the play between cage mates during the 35th day of life, which is the peak play period. Compared with LE rats reared with LE partners, LE rats reared with a F-344 partner, experience less play, with over 75% of playful attacks being initiated by the LE rat. Moreover, the F-344 rats were less likely to adopt defensive actions that promoted wrestling and so led to few opportunities for reciprocal exchanges (i.e., role reversals). Such reciprocity has been shown to be essential for training social skills during play fighting. These findings support the hypothesis that impoverished juvenile play experiences affect the development of executive functions and the social skills they support. Funding Acknowledgement:This work was supported by Natural Sciences and Engineering Research Council of Canada, Grant/Award Number: 2018-03706 to SMP

Speaker

Rachel Stark University of Lethbridge

Gabaergic neurons in the Medial nucleus of the Amygdala modulating Social Defensive behaviors

Sterde, Erika Tissiana[1]; Motta, Simone Cristina [1]. Department of Anatomy, ICB, University of São Paulo.
The medial nucleus of the amygdala (MeA) is crucial to social behaviors due to its role on olfactory processing. The posterodorsal portion (MeApd) is recruited during social defense and has a large proportion of gabaergic neurons. In this present study, we mapped the MeApd's efferents gabaergic projections and functionally investigated the MeA's gabaergic neurons in social defense. For the anatomical study we used transgenic male and female mice ($Vgat^{CRE}$), that received unilateral injection of the anterograde virus, AAV5.Ef1a.DIO.hCHR2 (H134R) EYFP into MeApd. For the functional study we used transgenic mice ($Vgat^{Flox}$) that had the gene of the GABA vesicular transporter ablated in the presence of CRE-recombinase enzyme. Here, animals were separated into control and experimental groups that received bilateral AAV injection (AAV.hSyn.EYFP or AAV5-CMV-CRE-GFP) into MeApd, and were exposed to the Resident-Intruder Paradigm. The results showed that the MeApd sends GABAergic

projections to the bed nuclei stria terminalis (BST), ventral premammilary nucleus (PMV). We did not find GABAergic MeApd projections to the ventromedial hypothalamic nucleus (VMH) and to medial preoptic nucleus (MPN), as previously described in the literature. The results of functional studies showed statistically significant behavioral changes (Student´s T Test) as follows: total time of social behaviors was higher in the experimental group when compared to the control group; higher total exploration time in the experimental group when compared to the control group; the experimental group expressed less defensive behavior when compared to the control group; and a decrease in total passive defense time when compared to the control group. We did not obtain statistically significant results between groups regarding bites received from the resident and total duration of active defense. Our results indicate that MeApd's gabaergic neurons modulate social defense, and the loss of gabaergic function directly affects the behaviors expressed in the face of an agonistic encounter with a conspecific. We also saw that it is possible that MeApd exerts its roles in social defense through BST or PMV. Ethics in animal research approval (CEUA, ICB-USP) # 58 / 2016. Funded By FAPESP # 2018/12763-2.

Speaker

Erika Sterde Institute of Biomedical Sciences from University of Sao Paulo (ICB/USP)

Next Generation In Situ Sequencing for Spatial Single-cell Analysis and Cell Typing in Intact Tissue Samples

Next Generation In Situ Sequencing for Spatial Single-cell Analysis and Cell Typing in Intact Tissue SamplesStergiadou, Johanna1; Rouault, Morgane1; Hernandez, Ivan1; Verheyen, Toon1; Bjorninen, Anton1; Hilscher, Markus1; Qian, Xiaoyan1; Kuhnemund, Malte1.1. CARTANA AB, Nobels VÃ¤g 16, 171 65 Solna, SwedenSingle cell RNA sequencing (scRNA-seq) has revolutionized the understanding of the complexity of tissues by dissecting the transcriptomic heterogeneity and revealing previously unknown cell types or cell states. However, scRNA-seq does not allow the visualization of spatial organization of single cells within the tissue. In order to overcome this limitation, spatial gene expression profiling technologies have emerged as a solution to localize molecularly defined cell types within their morphological context. The Next Generation In Situ Sequencing (ISS) technology from Cartana can rapidly analyse and visualize the expression of hundreds of targets within morphologically intact tissue samples at single-cell resolution. ISS takes place in intact morphologically tissue sections (Fresh Frozen and FFPE), targeting selected genes of interest. With the new high sensitivity library preparation kit, the RNA is targeted directly, instead of cDNA, increasing sensitivity with retained specificity (can even detect splice variants). Our new sequencing chemistry in our ISS kits generates higher signal-to-noise ratios that enables the detection of up to 600 genes simultaneously with very high throughput (10cm2 of tissue/week) and single-cell resolution. CARTANA is a Stockholm-based company that makes ISS available to the research community and pharma industry in the form of services and products. CARTANA currently offers ISS reagents kits with customized gene panels and services for cell type mapping in CNS and PNS samples (human and rodent).

Speaker

Johanna Stergiadou Field Scientist, CARTANA

Modulatory Role of Systemic and Septal Endocannabinoid

Modulatory Role of Systemic and Septal Endocannabinoid Signaling on Social Fear Extinction. Theresa Suess 1, Rohit Menon 1, Anna Bludau 1, Inga D Neumann 1. 1 Department of Behavioral and Molecular Neurobiology, University of Regensburg. Social anxiety disorder is the second most common anxiety disorder, but current treatments are still rather unspecific. An important modulator of traumatic memories and social behavior is the endocannabinoid (eCB) system. However, to which extend the eCB system is involved in the development of social fear is largely unknown. Therefore, male CD1 mice were exposed to the social fear conditioning paradigm (resembling social anxiety disorder in humans) in combination with

pharmacological manipulation of the eCB system to investigate the consequences on social anxiety behavior. The cannabinoid receptor type 1 (CB1R) was targeted by intraperitoneal (i.p.) Administration of the CB1R inverse agonist AM251 (1 mg/kg) 30 min before social fear extinction training. AM251 significantly impaired social fear extinction, suggesting that eCB signaling via the CB1R is involved in the extinction of social fear. A partial agonist of cannabinoid receptors is delta-9-tetrahydrocannabinol (THC), which was applied i.p. either in a low dose (LD) (1 mg/kg) or a high dose (HD) (5 mg/kg) 30 min prior to extinction of social fear. Neither the LD-, nor the HD of THC did alter social investigation time in conditioned mice, compared to vehicle-treated controls, demonstrating that systemic THC does not influence social fear extinction in mice, when administered prior to extinction training. However, at HD, THC increased anxiety-like behavior in the open field test. A region that is involved in the expression and extinction of social fear is the lateral Septum (LS). Aiming to elevate eCB levels in the LS, JJKK048 (inhibitor of 2-arachidonylglycerol (2-AG) degradation) or URB597 (inhibitor of N-arachidonoylethanolamine (AEA degradation) were bilaterally infused (10 ng/hemisphere) 15 min prior to social fear extinction. Neither JJKK048, nor URB597 affected social investigation time, suggesting that either 2-AG and AEA levels are not elevated in the LS following social fear conditioning or respective enzymes are not active. The results of this study provide first evidence for the involvement of the eCB system in the regulation of social fear and its extinction. Supported by Deutsche Forschungsgemeinschaft (Ne465-33-1; GRK 2174)

Speaker

Theresa Suess University of Regensburg

Decreased expression of Proteolipid Protein-1 (PLP-1) and altered inflammatory regulation accompany aberrant behaviors of mice deficient for brain-specific gangliosides

Decreased expression of Proteolipid Protein-1 (PLP-1) and altered inflammatory regulation accompany aberrant behaviors of mice deficient for brain-specific gangliosides. Evgeniy Svirin 1,2, Ekaterina Veniaminova 1, Ekaterina Kopeikina 3, Tatyana Veremeyko 3, Amanda W.Y. Yung 3, Shawn Zheng Kai Tan 4, Sharafuddin Khairuddin 4, Klaus-Peter Lesch 1, 2,5, Lee Wei Lim 4, Tatyana Strekalova 1,2,5, Eugene D. Ponomarev 3.1 Sechenov First Moscow State Medical University, Moscow, Russia, 2 Maastricht University, Maastricht, The Netherlands, 3 The Chinese University of Hong Kong, Hong Kong, 4 Hong Kong University, Hong Kong, 5 University of WÃ¼rzburg, WÃ¼rzburg, Germany. Lactosylceramide alpha-2,3-sialyltransferase (ST3GAL5) is a key enzyme in the biosynthesis of brain-specific gangliosides; SNVs of ST3GAL5 are related to neurological and neuropsychiatric morbidity. ST3GAL5 dysfunction is re-capitulated in recently generated St3gal5âˆ’/âˆ’ mice, whose features were not yet studied in a detail and were addressed in our work. Mutants of both sexes have shown motor deficits, elevated anxiety-like behavior, impaired conditioned taste aversion. Male mutants displayed elevated aggression and hyperlocomotion. Gene expression of interleukin (IL)-1Î² was elevated the brain and the spleen, and brain expression of myelin marker PLP-1 was decreased in both sexes, among other changes, including altered expression of tumour necrosis factor (TNF) and IL-6. The administration of lipopolysaccharide (LPS, 0.1 mg/kg) has evoked blunted over-expression of IL-1Î² and increased aggressive/dominant behaviours in male mutants, and the opposite changes in female mutants, in comparison with controls. Thus, genetic deficiency of St3gal5 results in motor deficits and signs of dysmyelination and neuroinflammation, gender-dependent manifestations of anxiety, hyperlocolomtion, cognitive impairment and altered response to systemic inflammation. The work was funded by Research Grant Council - Areas of Excellence Fund from Hong Kong government (AoE/M-604/16) and by the 'œ5-100' Russian Academic Excellence Program.

Speaker

Evgeniy Svirin Sechenov First Moscow State Medical University, Moscow, Russia

DBS-like optogenetic stimulation of the nucleus accumbens attenuates cocaine reinstatement

DBS-like optogenetic stimulation of the nucleus accumbens attenuates cocaine reinstatement. Sarah E. Swinford-Jackson 1, Matthew T. Rich 1, Phillip J. Huffman 2, Melissa C. Knouse 2, Arthur S. Thomas 2, R. Christopher Pierce 1. 1 Brain Health Institute, Department of Psychiatry, Robert Wood Johnson Medical School, Rutgers University, Piscataway, NJ, USA. 2 Center for Neurobiology and Behavior, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. Deep brain stimulation (DBS) of the nucleus accumbens (NAc) shell attenuates reinstatement of cocaine-seeking in rats. However, the potential differential impact of DBS on specific populations of neurons to drive the suppression of cocaine-seeking is unknown. Medium spiny neurons in the NAc are differentiated by the expression of dopamine D1 receptors (D1DRs) or dopamine D2 receptors (D2DRs), activation of which promotes or inhibits cocaine-seeking behavior, respectively. We tested the hypothesis that DBS-like optogenetic stimulation of D1DR-containing neurons in the NAc shell would potentiate cocaine-primed reinstatement, whereas DBS-like optogenetic stimulation of D2DR-containing neurons in the NAc shell would attenuate cocaine-primed reinstatement. High frequency, DBS-like optogenetic stimulation of D2DR-containing neurons attenuated reinstatement of cocaine seeking in male rats, whereas DBS-like optogenetic stimulation of D1DR-containing neurons did not alter cocaine-primed reinstatement. These results suggest that DBS of the NAc attenuates cocaine-primed reinstatement through the selective manipulation of D2DR-containing neurons. Supported by NIH grants R01 DA015215 and T32 DA028874.

Speaker

Sarah Swinford-Jackson Rutgers University

Open access big data from a standardized rodent paradigm in behavioral neuroscience research on the organization and disorganization of behavior

Open access big data from a standardized rodent paradigm in behavioral neuroscience research on the organization and disorganization of behavior. Szechtman, Henry1; Dvorkin-Gheva, Anna1; Gomez-Marin, Alex2. 1 McMaster University, Canada; 2 Instituto de Neurociencias de Alicante, Spain. Behavioral Neuroscience utilizes methods from many different disciplines to uncover the organizational principles of behavior and its neurobiological roots. Progress in behavioral neuroscience research is marked by successful inclusion of new technologies in the methodological toolkit. The emerging machine learning techniques should be of value to research on behavior and its neurobiology and to research on mechanisms of psychiatric disorders using animal models. However, those techniques depend on large dataset inputs, generally unattainable with typical behavioral neuroscience experiments. That difficulty is surmountable by collating over time the data from many different laboratories and studies, sharing a standardized protocol. Over the last 3 decades, we employed in our work on an animal model of obsessive-compulsive disorder (OCD) a standardized paradigm and run over 1700 subjects for a total of nearly 20500 trials, each 55 min in duration thus yielding nearly 19000 hr of testing in a large open field. As part of the standardized protocol, each trial was video-recorded by an overhead camera, the position of the rat's body center of mass extracted from the video records via computer vision algorithms, and the obtained track files were subsequently processed using custom software to obtain measures of compulsive checking and locomotion. We have collated the available video and track files, renamed these records according to a structured nomenclature, organized the files into a structured directory tree, and are annotating meta-variables of each trial. The complete dataset will be published and available for analysis in novel ways, including extraction from the videos of any postural information of the rat and measures of ritual behavior of relevance to OCD. The comprehensive meta-variables will allow researchers to design their own study by selecting the pertinent trials from the available pool of records. It is suggested that our very large dataset can be the seed for an organized effort to build a comprehensive database of behavioral experiments that further research on the organization and disorganization of behavior. Dataset studies funded by CIHR, OMHF and NSERC

Speaker

Henry Szechtman Professor, McMaster University

Binge-drinking during middle age perturbs reversal learning while sparing spatial and working memory: Results from a pilot study of a heterogenous cohort of mice

Binge-drinking during middle age perturbs reversal learning while sparing spatial and working memory: Results from a pilot study of a heterogenous cohort of miceKaren K. Szumlinski 1 Eliyana Van Doren 1, Leonardo Jimenez Chavez 1, Jacob Matalon 1, Emely Rivera 1.1. University of California Santa BarbaraExcessive alcohol consumption damages the brain with accumulating evidence implicating alcohol abuse in dementia etiology. Binge-drinking is defined as alcohol consumption within approximately 2 h that elevates blood alcohol concentration above 80 mg/dL. While binge-drinking is most pronounced in adolescents and young adults, it is also prevalent in older adults, particularly the middle-aged. Here, a pilot study characterized binge-drinking in middle-aged mice (5-8 months of age) and its effects upon spatial and working memory. For this, middle-aged male and female mice on either an isogenic C57BL/6J or congenic C57BL/6J background were subjected to multi-bottle, 2-h, Drinking-in-the-Dark (DID) procedures for 30 days. Two days following the end of drinking, mice were trained and tested in a Morris water maze and then trained to locate 4 hidden platforms in a water version of the radial arm maze. Alcohol intake escalated progressively in middle-aged mice, with no sex differences. Blood alcohol concentrations were at or above 80 mg/dL, indicating binge-drinking. Relative to water controls, binging mice were impaired in their ability to locate a visible platform in the Morris maze, but were marginally more successful at locating the hidden platform. However, when the hidden platform was relocated, binging males had more difficulty locating the new platform position than water controls, with no binge-drinking effect observed in females. In the radial arm maze, female bingers required more training sessions to acquire the maze than their water counterparts, but otherwise no group differences were observed with respect to radial arm maze performance. While confounded by a range of ages and genetic heterogeneity, these data indicate that middle-aged male and female mice engage in binge-drinking under DID procedures. However, it appears that a 1-month history of binge-drinking during middle-age negatively impacts reversal learning, while sparing spatial and working memory. Current studies seek to replicate these findings in a uniform sample of C57BL/6J mice. Funding provided by NIH/NIAAA grant AA024044 to KKS, NSF Predoctoral Fellowship to C.L.J.C.

Speaker

Karen K. Szumlinski Professor, Department of Psychological and Brain Sciences, University of California Santa Barbara

Moms, less deserving of research? The role of enriched environment in rodent dams' maternal, anxiety and depression-like behaviour: A scoping review

Moms, less deserving of research? The role of enriched environment in rodent dams' maternal, anxiety and depression-like behaviour: A scoping review. Talbot,Joey, Barbeau,Kheana, Boileau,Kayla, Sparling,Jessica E, Konkle,Anne TM. Interdisciplinary School of Health Sciences, University of Ottawa. The literature suggests that an enriched environment can have behavioural implications in rodents. Environmental enrichment is considered when physical changes are made to standard housing; these can be mechanical and/or social in nature. In the context of motherhood, the environment may be associated with physiological changes that could impact maternal behaviours and consequently, offspring neurodevelopment. Thus, the aim of this scoping review was to identify trends and themes in the literature over the past decade, regarding the effects of enriched environments on rodent maternal, anxiety and depression-like behaviours. Five databases were searched, 17 studies were identified. Twelve pertained to maternal behaviours, three looked at the effects on anxiety-like behaviours and two on depressive-like behaviours. Tools used to assess anxiety- and depressive-like behaviours were the elevated plus maze, open-field test, light-dark box, force swim test and the sucrose preference test. However, these models have only been validated with animals reared in standard laboratory settings which could impact the reliability and validity of the paradigms when paired with environmental manipulations. Our findings yield conflicting results on the topic of maternal behaviours and mixed results for anxiety- and depressive-like behaviours; some of these variations may be a consequence of standardization of the enriched environments. Our results speak to the need for standardizing enriched environments and for validating behavioural tests using animals housed in non-standard conditions.

Speaker

Joey Talbot Graduate Sudent, University of Ottawa

Effects of familiarity on behavioural complexity and dyad task performance: A pilot study

Effects of familiarity on behavioural complexity and dyad task performance: A pilot study. Talbot,Joey, Charron,Valerie, Plamondon,Helene. School of Psychology Department of Neuroscience University of Ottawa. From an evolutionary perspective, prosocial behaviours have contributed to many social species' survival as it allowed groups to work and help each other. Typically, in the wild, animals tend to help others from the same group as helping other species competing for the same resources may be maladaptive. Familiarity, a concept that is often used in behavioural research is based on the idea that animals will have a higher predisposition to help a familiar congener versus a stranger. Rodent models, especially dyad based tasks, allow us to study and understand this complex phenomenon involved in prosocial behaviours. Performance alone, usually assessed with lever presses or rewards given, cannot be used to understand these types of behaviours as they are limited in their inferential capabilities. Thus, other types of data such as behaviour analysis, is necessary to better understand prosocial behaviours. This study had two phases, the first one being a cagemate accompanying the actor rat (n= 6) then the second phase being a stranger rat accompanying the actor rat (n=3). The goal of this pilot study was to assess whether a rat would help a stranger compared to a cagemate in a prosocial setting. The task consisted of a two-chamber operant box, with one chamber that had accessibility to two levers, the easy lever (35 g of pressure) delivering one pellet to the actor rat and the hard lever (75 g of pressure) delivering one pellet to the actor and one to the rat in the other compartment. Behaviours were coded using the Boris coding software and analysed using the IBM's SPSS 23 software. While the results from the lever performance are showing a higher tendency for the actors to help their congener over a stranger, behavioural analysis shows that there are no notable and significant differences in the manner in which rats behave between each other (e.g. communication, deciding which lever to press), regardless of familiarity. Based on these preliminary results, familiarity does not appear to be a modulating factor in behavioural interactions in a prosocial dyad based operant task. This also indicates that further research is needed to better understand familiarity as a modulator in prosocial scenarios.

Speaker

Joey Talbot Graduate Sudent, University of Ottawa

Divergent pathways mediate 5-HT1A receptor agonist effects on close social interaction, grooming and aggressive behaviour in mice: exploring the involvement of the oxytocin and vasopressin systems

Divergent pathways mediate 5-HT1A receptor agonist effects on close social interaction, grooming and aggressive behaviour in mice: exploring the involvement of the oxytocin and vasopressin systemsAuthors: Oliver Tan1,2, Lewis J Martin1,2, Michael T Bowen1,2,*1 The University of Sydney, Brain and Mind Centre, Sydney, New South Wales, Australia2 The University of Sydney, Faculty of Science, School of Psychology, Sydney, New South Wales, Australia Background: 5-HT1A receptor (5-HT1AR) abnormalities are implicated in aggression and there has been considerable interest in developing 5-HT1AR agonists for treating aggression. Endogenous oxytocin (OXT) released upon stimulation of 5-HT1ARs in the hypothalamus mediates at least some of the effects of 5-HT1AR agonists on social behaviour. Aims: Given 5-HT1AR, OXT receptor (OXTR) and vasopressin V1a receptor (V1aR) agonists can all reduce aggression, the current study aimed to determine whether the anti-aggressive effects of 5-HT1AR stimulation can also be explained by downstream actions at OXTRs and/or V1aRs in a mouse model of non-territorial, hyper-aggressive behaviour. Methods: Male Swiss mice (N=80) were socially isolated or group housed for 6 weeks prior to the start of testing. Testing involved placing two unfamiliar weight- and condition-matched mice together in a neutral context for 10 min. Results: Social isolation led to a pronounced increase in aggressive behaviour,

which was dose-dependently inhibited by the 5-HT1AR agonist 8-OH-DPAT (0.1, 0.3, 1 mg/kg i.p.) with accompanying increases in close social contact (huddling) and grooming. The effects of 8-OH-DPAT on aggression, huddling and grooming were blocked by pre-treatment with a selective 5-HT1AR antagonist (WAY-100635, 0.1 mg/kg i.p.). The anti-aggressive effects of 8-OH-DPAT were unaffected by an OXTR antagonist (L-368,899, 10 mg/kg i.p.), whereas the effects on huddling and grooming were inhibited. Pre-treatment with a V1aR antagonist (SR49059, 20 mg/kg i.p.) had no effect. Conclusions: Our study suggests that stimulation of endogenous oxytocin is involved in the effects of 5-HT1AR activation on close social contact and grooming but not aggression.Funding and AcknowledgementsThis work was supported by Australian National Health and Medical Research Council (1092046, 1166044) funding to MTB.

Speaker

Oliver Tan The University of Sydney

Higher baseline lateral habenula firing correlates with decreased motivation to seek ethanol over time

Higher baseline lateral habenula firing correlates with decreased motivation to seek ethanol over time Shashank Tandon, University of UtahMany people consume alcohol, yet only some vulnerable individuals develop alcohol use disorder (AUD). Variability in the risk for alcohol abuse is multifactorial and includes differences in behavioral traits. The lateral habenula (LHb) has been shown to mediate aversive state-related behavioral responses. Interestingly, in both humans and rodents, depression-like symptoms are associated with high LHb activity. Additionally, there is a high co-morbidity between major depressive disorder and AUD in humans. Thus, we wanted to understand whether individual variation in LHb activity and behavioral state in ethanol-naÃ¯ve rats affect their home-cage ethanol drinking patterns. Hence, in this study, we determined the correlation between individual variability in baseline LHb neural activity, the negative-affective state-related ultrasonic vocalizations (USVs; 22-28 kHz), and the extent of ethanol use over time. To do so, we surgically implanted a unilateral 16-wire electrode array in the LHb of adult male Long Evans rats (n=11). Rats were placed in sound-insulated chambers for two hours, where they were free to explore while we simultaneously recorded neuronal signals from their LHb and their ultrasonic vocalizations. Next, these rats underwent an intermittent access to ethanol (IAE) paradigm, where they received 20% ethanol for 24 hours on alternate days and ad-libitum water in their home cages for four weeks. The change in ethanol intake over time differed between rats, with some rats escalating their ethanol intake in the four weeks, while other rats showed no meaningful change in ethanol intake over time as compared to the first session. We found a significant negative correlation between average LHb firing rates and changes in ethanol intake in the first week of IAE, such that rats with higher baseline LHb activity did not escalate their ethanol intake with more sessions. We also found a weak positive correlation between the number of 22-28 kHz USVs and the average LHb firing rates of these rats. These results indicate that higher baseline LHb neuronal activity in individual rats is associated with decreased motivation to seek ethanol during the early stages of ethanol consumption. NIAAA RO3 AA026758-01A1

Speaker

Shashank Tandon University of Utah

Chemogenetic activation of Gi signaling in dorsal hippocampal astrocytes prevents object memory consolidation in ovariectomized female mice

Chemogenetic activation of Gi signaling in dorsal hippocampal astrocytes prevents object memory consolidation in ovariectomized female mice. Lisa R. Taxier, Sarah M. Philippi, Karyn M. Frick. University of Wisconsin-Milwaukee, Department of Psychology. Astrocytes, despite being the most abundant cell type in the brain, have historically been relegated to a supportive role in the central nervous system. However, recent evidence suggests a more active role for astrocytes in synaptic activity in brain regions like the

hippocampus. To test whether dorsal hippocampal (DH) astrocytic activity impacts memory consolidation, we used Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to manipulate Gi signaling in DH astrocytes. Nine week-old ovariectomized female C57BL/6 mice were infused into the DH with control viral construct (AAV-GFAP-eGFP) or hM4Di-containing viral construct (pAAV-GFAP-HAhM4D(Gi)-IRES-mCitrine) (n=10-12/group). Two weeks following viral delivery, mice were trained and tested in the object recognition (OR) and object placement (OP) tasks to assess object recognition and spatial memory consolidation, respectively. Immediately after training in each task, mice received an intraperitoneal (i.p.) injection of the DREADD actuator Clozapine-N-Oxide (CNO), and were then tested 24 h (OR) or 4 h (OP) later. Here, we tested effects of two doses of CNO, 1 and 5 mg/kg. hM4Di-infused mice injected post-training with 5 mg/kg CNO exhibited impaired OR and OP memory relative to mice expressing control virus, suggesting that activation of Gi signaling in DH astrocytes blocks object recognition and spatial memory consolidation. Two weeks later, mice were retrained with novel objects, received a 1 mg/kg post-training i.p. injection of CNO, and were tested at the same delays as before. The 1 mg/kg dose of CNO did not impair OR and OP memory in mice expressing hM4Di virus relative to chance levels of performance or to GFP-expressing controls. This dose will therefore be used in future studies to determine if activation of astocytic Gi signaling interferes with the memory-enhancing effects of neuromodulators. Combined, these data suggest that activating Gi signaling in DH astrocytes with a sufficiently high dose of CNO impairs object memory consolidation. Supported by NIH Grants R01MH107886 and 1F31MH1188222-01A1, and Alzheimer's Association SAGA-17-419092.

Speaker

Lisa Taxier Graduate Research Assistant, University of Wisconsin-Milwaukee

Establishing a rodent behavioural model of cognitive reserve

Establishing a rodent behavioural model of cognitive reserve. Terstege, Dylan J; Durante, Isabella; Epp, Jonathan R. University of Calgary. When faced with neuronal damage or degeneration, not all individuals display the same degree of cognitive impairment. Variables linked to cognitive exercise, such as number of years of formal education, and participation in cognitively stimulating activities, are correlated with increased resiliency to neurodegeneration. As this resiliency correlates with cumulative cognitive stimulation over the course of a lifetime, it is known as the development of a cognitive reserve. Cognitive reserve also appears to preserve cognitive functions in face of the declines that are typical with normal aging. To understand the underpinnings of this phenomenon we have established a mouse model of cognitive exercise. One group of mice underwent a 3-month Morris water task training protocol consisting of 4 daily sessions per week of 4 trials per day. We used a moving platform version of the task in which the hidden escape platform was cycled between one of ten locations after every second day. A second group of mice spent this time in standard housing conditions. A third yoked control group of animals swam for the same amount of time as the cognitive training group but there was no escape platform in the pool. Following the conclusion of the training protocol, animals were tested in a contextual fear conditioning task. With percent freezing as a proxy for memory ability, we found that the yoked control and cage control groups had comparable rates of freezing. The mice that received cognitive training displayed increased freezing during the first half of the context memory test in anticipation of the foot-shock but then showed an increased rate of fear memory extinction. These results suggest that the cognitive training increased memory ability and flexibility. The functional networks underlying these behaviours were analyzed using correlated regional cfos density and graph theoretical analysis. Cognitive training resulted in an overall increase in global efficiency. WE also observed a large increase in the node degree of the retrosplenial cortex. The functional connectivity of the retrosplenial cortex may be used as a predictor of successful cognitive aging. Our results indicate that cognitive exercise can enhance memory performance and alter both local and global network connectivity. Funding: NSERC, Brain Canada/Azrieli Foundation.

Speaker

Dylan Terstege University of Calgary

Conditioned place preference for cocaine in mice lacking vesicular zinc.

Conditioned place preference for cocaine in mice lacking vesicular zinc. Thackray, Sarah E., 1, Fu, Selena, 1, Dyck, Richard H., 1. 1 University of Calgary. Zinc (Zn) is an important component of all cells in the body where it has a variety of structural and functional roles. A subset of Zn in the brain has been shown to act as a neurotransmitter in several regions including the hippocampus and somatosensory cortex. This so-called vesicular Zn, due to its ability to be loaded into vesicles and released in an activity-dependent manner, is thought to be critical for experience-dependent synaptic plasticity. Brain regions involved in the reward pathway, including the ventral striatum and prefrontal cortex, contain high amounts of vesicular Zn; however, its role there has not been studied. The purpose of this study was to probe the role of vesicular Zn in the reward pathway. Specifically, we compared male and female Zn transporter 3 (ZnT3) knockout (KO) mice, which lack the gene and thus the transporter solely responsible for loading Zn into vesicles, to wildtype (WT) mice on a conditioned place preference (CPP) task using cocaine. Studies show that Zn interacts with and augments cocaine's action on the dopamine transporter. The task included pairing saline and cocaine (20 mg/kg) with different environmental contexts (striped walls vs polka dot walls) over alternating days. Test sessions with free exploration of both environments were conducted before drug, after 2 drug-chamber pairings (Test 1), after 4 drug-chamber pairings (Test 2) and again 1 week after drug-chamber pairings were completed (Test 3). Findings suggest that ZnT3 mice form a CPP for cocaine, however, males irrespective of genotype can form the CPP after 2 drug-chamber pairings, while females require 4 pairings. Female KO mice did not show a significant CPP on any tests. Male KO mice showed significant CPP on Tests 1 and 2, but not Test 3, suggesting that while they are able to form CPP, these are not retained beyond the duration of the drug-chamber pairings. Effect sizes suggest that both male and female WT mice retained the CPP one week after drug-chamber pairing sessions finished. In conclusion, vesicular Zn appears to play a critical role in forming CPP to cocaine; however, it does so in a sex-dependent manner. In females, it seems critical for the formation of a CPP in general, while in males, it is needed to maintain the CPP beyond the scope of the drug-chamber pairing sessions.

Speaker

Sarah Thackray PhD Student, University of Calgary

The neurobiological mechanisms underlying cephalopod behavioural change at elevated CO2 levels

The neurobiological mechanisms underlying cephalopod behavioural change at elevated CO2 levels. Jodi T Thomas 1, Blake L Spady 2, Philip L Munday 1, Sue-Ann Watson 1, 3. 1 ARC Centre of Excellence for Coral Reef Studies, James Cook University, Queensland, Australia, 2 College of Science and Engineering, James Cook University, Queensland, Australia, 3 Biodiversity and Geoscience Program, Museum of Tropical Queensland, Queensland Museum, Queensland, Australia. Anthropogenic carbon dioxide (CO2) emissions are being absorbed by the oceans. CO2 levels projected to occur in the ocean by the end of this century can alter a range of behaviours in fish and marine invertebrates. Disrupted functioning of the Î³-aminobutyric acid type A (GABA-A) receptor is suggested to underlie elevated CO2-induced behavioural changes in fish. However, little is known about the effects of elevated CO2 levels on the function of GABA-A-like receptors and other ligand-gated chloride channels in marine invertebrates. We examined the conspecific-directed behaviours and activity levels of a cephalopod mollusc, the two-toned pygmy squid Idiosepius pygmaeus, when exposed to a mirror after seven days in current-day or projected end-of-century CO2 conditions. Control and elevated CO2 squid were randomly assigned to a sham, gabazine (GABA-A receptor antagonist) or picrotoxin (chloride channel blocker) treatment immediately before behavioural testing. If disrupted function of GABA-A-like receptors and/or other ligand-gated chloride channels underlies altered behaviours at elevated CO2, we predicted that treatments with gabazine or picrotoxin should reverse the behavioural effects seen in elevated CO2 treatments. Elevated CO2 increased squid activity levels and altered some, but had no meaningful effect on other, conspecific-directed behaviours. Gabazine and picrotoxin treatment partially reversed the effect of elevated CO2 on some, but not other, behavioural measures. Our results suggest that GABA-A-like receptors and ligand-gated chloride channels may underlie some behavioural changes at elevated CO2 in I. pygmaeus. Multiple mechanisms are likely involved, which may explain the variability in the effects of elevated CO2 and drug treatment among behavioural traits. This study highlights the potential complexity of the mechanisms underlying behavioural change at elevated CO2 in marine

invertebrates. Funding: James Cook University and ARC Centre of Excellence for Coral Reef Studies.

Speaker

Jodi Thomas PhD Candidate, ARC CoE for Coral Reef Studies, James Cook University

Impairments in trace eyeblink conditioning occur early in the lifespan: A behavioral biomarker for hippocampal dysfunction with implications for dementias

Impairments in trace eyeblink conditioning occur early in the lifespan: A behavioral biomarker for hippocampal dysfunction with implications for dementias. Thompson, L.T.; West, R.M.; Lea, P. Neuroscience, University of Texas at Dallas. Eyeblink conditioning (EBC) is an established model to assess learning within and across species. In animal models and in humans, trace EBC requires intact hippocampal function for successful acquisition. While impairments in trace EBC are well known in advanced aging (i.e. humans > 65 yr), the current cross-sectional study examined both age and severity of onset of impaired acquisition of trace EBC in humans from a general population. Methods: 80 healthy individuals, aged 19 ‴ 88 yr (32 M, 48 F) were recruited and divided into age deciles (i.e. 30-39, 40-49). All subjects had normal hearing and responded to airpuffs (described below) with unconditioned eyeblinks. 60 trace conditioning trials each were presented. Airpuffs (150 ms, 3 psi) to the left cornea served as unconditioned stimuli (US), and tones (100 ms) served as conditioned stimuli (CS), separated by 500 ms interstimulus trace intervals. An infrared detector was used to blindly score trial performances, and intertrial intervals varied, mean 15 s. Mean percent CRs (i.e. eyeblinks timed to shield the cornea from the US) served as the primary acquisition measure. Percent CRs were compared within and between age groups using one-way ANOVA and Tukey's post-hoc comparisons. Results: No significant sex-differences were found in mean percent CRs across ages (p=0.64). 20- and 30-year-old age groups exhibited similar high percentages of CR acquisition (p=0.8), and performed significantly better than older cohorts (p=0.01). Significant deficits in trace EBC acquisition were observed in the age group 40-49 yr, considerably earlier in the lifespan than previously suspected. In 40 yr or older individuals, trials-to-40% CRs were significantly slowed, and the percentage of the population exhibiting severe impairments acquiring the CR significantly increased. After age 40, impaired acquisition was observed consistently early (before trial 25) compared to younger subjects, indicating significant hippocampal dysfunction. Potential clinical applications, with an emphasis on dementing disorders like Alzheimer's that exhibit early hippocampal degeneration, are discussed. Funded by the Clark and the Buhrmester Foundations, and BBS Research Initiatives.

Speaker

Lucien "Tres" Thompson NSC Program Head, Dept. of Neuroscience, University of Texas at Dallas

The role of dopaminergic projections to the orbitofrontal cortex in decision-making

The role of dopaminergic projections to the orbitofrontal cortex in decision-making Thompson, Shannon M.1 , Tapp, Danielle1, and McMurray, Matthew S.1 1. Miami University, Department of Psychology. Decision-making requires many encoded signals, like reward, motivation, memory, and emotion. One prominent neurobiological pathway involved in decision-making is the mesocortical system, comprised of the ventral tegmental area's dopaminergic projections to the prefrontal cortex. This circuit is commonly associated with learning, reward, and executive function. Though the ventral tegmental area projects to many subregions of the prefrontal cortex, specific subregions like the orbitofrontal cortex are thought to encode information in a more granular way, such as the value of available options. However, it is unknown if dopaminergic projections to the orbitofrontal cortex contribute to value encoding. Outcome value is determined by both the magnitude of the reward and animal need, therefore we hypothesized that reward signals from the ventral tegmental area to the orbitofrontal cortex would be critical to value estimation. To test this hypothesis, we lesioned the orbitofrontal cortex's dopaminergic afferents using 6-hydroxydopamine in rats and assessed its effect on decision-making using three paradigms in which the

value of reward is altered. The first task, probabilistic discounting, gave animals the choice between a small certain reward and a large uncertain reward, delivered at decreasing probability. Probability was held constant each day, but decreased over days of testing to devalue the large outcome. The second task, delay discounting, devalued the large outcome by increasing the time between lever press and large reward delivery. The delay was held constant within each session, but decreased over days. Finally, reversal learning, devalued an outcome by swapping which lever delivers reward, thereby requiring a flexible change in the behavioral response. Our results showed no differences between lesion and control animals in any of our tasks. This suggests that dopaminergic projections to the orbitofrontal cortex may not be involved in value encoding, that our lesion location may not have been accurate, or that adaptation to the lesion may obscure its effects. Using a more temporally precise means of inhibiting/observing the circuit, such as chemogenetics, optogenetics, or photometry, may provide a clearer picture of the circuit's role in value encoding.

Speaker

Shannon Michele Thompson Graduate student in the Psychology Ph.D. Program., Miami University

Effects of the testicular feminization mutation (Tfm) of the androgen receptor gene on social behavior in mice

Effects of the testicular feminization mutation of the androgen receptor gene on social behavior in mice. Darren Leung, Junho Lee, Adren Blanco, and Houng-Wei Tsai. Department of Biological Sciences, California State University Long Beach, Long Beach CA 90840, USA. Androgens influence different behavioral responses between the sexes. In rodents, behavioral masculinization is believed to result from (1) early exposure to testosterone (T) during development that organizes the neural circuits underlying male-specific behaviors (organizational effect) and (2) the presence of T in adulthood that activates the previously masculinized neural machinery (activational effect). While androgen receptor (AR)-mediated androgen actions are necessary for the display of both sexual and aggressive behaviors in male mice, it still remains unclear to what extent AR is involved in the development and control of sexually dimorphic social behavior. To address this, we used male mice carrying the testicular feminization mutation (Tfm) in the Ar gene to assess the role of the AR with respect to sex differences of sociability. At 3-7 months of age, Tfm mice and their wild-type (WT) littermates (n=15-18 per group) were subjected to a sociability test, in which a subject was video-recorded for the interaction with a wire-mesh corral containing an unfamiliar, intact conspecific of the same or opposite sex (social stimulus) v.s. an empty one (non-social stimulus) for 15 min. We have found that regardless of sex or genotype, all subjects spent more time in the close vicinity of a social stimulus than the non-social compartment ($p<0.05$). Interestingly, WT males spent more time exploring the female stimulus than WT females ($p<0.05$) while the amount of time Tfm males spent was intermediate between the two WT groups. When exposed to a male stimulus, no difference was observed between WT males and females, but Tfm males, relative to WT males, spent less time around the social stimulus ($p<0.05$). Additionally, the sex difference in sociability was not a result of increased ambulation, but surprisingly, females displayed longer travel distance than WT and Tfm males ($p<0.05$). Based on our results, we conclude that sociability is sexually dimorphic in mice, which depends on the sex of the stimulus mouse, and AR is partially responsible for the masculinization of this behavioral task. Acknowledgement: This project was supported by the NIH grant (5UL1GM118979) and CSUPERB Research Development grant.

Speaker

Houng-Wei Tsai Associate Professor, California State University, Long Beach

A dopamine-induced gene expression signature regulates neuronal function and cocaine response.

A dopamine-induced gene expression signature regulates neuronal function and cocaine response. Jennifer

J. Tuscher 1, Katherine E. Savell 2, Morgan E. Zipperly 1, Corey G. Duke 1, Robert A. Phillips III 1, Allison J. Bauman 1, Saakshi Thukral 1, Faraz A. Sultan 1, Nicholas A. Goska 1, Lara Ianov 1, & Jeremy J. Day 1. 1. University of Alabama, Birmingham, 2. National Institute on Drug Abuse. Drug addiction is a worldwide health problem, with overdose rates of both psychostimulants and opioids currently on the rise in many developed countries. Drugs of abuse elevate dopamine levels in the nucleus accumbens (NAc) and alter transcriptional programs believed to promote long-lasting synaptic and behavioral adaptations. However, even with well-studied drugs such as cocaine, drug-induced transcriptional responses remain poorly understood. This is in part due to the cellular heterogeneity of the NAc, which contains multiple neuronal and non-neuronal cell types, and the complex actions induced by drugs of abuse via multiple neurotransmitter systems. Here, we leveraged single-nucleus RNA-sequencing to generate a molecular atlas of cell subtypes in the NAc, defining both sex-specific and cell type-specific responses to acute cocaine experience in a rat model system. Using this transcriptional map, we identified specific neuronal subpopulations that are activated by cocaine, and defined an immediate early gene expression program that is upregulated following cocaine experience in vivo and dopamine (DA) receptor activation in vitro. To further explore the neuronal response to this DA-induced gene expression signature, we engineered a large-scale CRISPR/dCas9 activation strategy to recreate this program. Multiplexed induction of this gene program initiated a secondary synapse-centric transcriptional profile, altered striatal physiology in vitro, and potentiated cocaine sensitization in vivo. Taken together, these results define the genome-wide transcriptional response to cocaine with cellular-level precision, and demonstrate that drug-responsive gene programs can potentiate both physiological and behavioral adaptations to drugs of abuse. This research was supported by NIH grants DA039650, DA034681, MH114990, DA042514, and DA04177. Thank you to IBNS for travel funding to support the presentation of this work.

Speaker

Jennifer Tuscher Postdoc, University of Alabama, Birmingham

ER-beta but not ER-alpha participates in the antidepressant-like effect of an aqueous extract of pomegranate in an animal model of menopause

ER-beta but not ER-alpha participates in the antidepressant-like effect of an aqueous extract of pomegranate in an animal model of menopause. 1Brenda ValdÃ©s-Sustaita, 2Erika Estrada-Camarena,1Carolina LÃ³pez-Rubalcava, 2MarÃa Eva GonzÃ¡lez-Trujano, 1Cinvestav-IPN, 2INPRFM. Pomegranate has a high content of polyphenols (mainly ellagitannins, which can be biotransformed into active compounds by gut microbiota metabolism) and other phytoestrogens that not requires biotransformation that also confer potent estrogenic actions. Recently, an aqueous extract of pomegranate (AE-PG) demonstrated antidepressant-like actions mediated by estrogen receptors (ER) in rats with estrogen deprivation, suggesting its potential to function as an alternative to estrogen replacement therapy in menopause-related depression treatment. However, up to date, the activity of the extract as an antidepressant linked to estrogen receptors has not been studied and therefore it is necessary to conduct investigations into it since it would offer advantages over traditional treatments with phytoestrogens. Hence, the first aim of this study was to determine if AE-PG needs to be metabolized by gut microbiota to produce its antidepressant-like effect. Thus, different doses of AE-PG (1 and 10 mg/kg) were administered by oral or intraperitoneal route to ovariectomized female Wistar rats that were tested in the forced swimming test (FST). Thereafter, the second aim of this work was to determine whether the antidepressant-like effect was mediated by a specific ER-subtype (ERa or ERb), so the antidepressant-like effect of the minimum effective dose of the EA-PG (1 mg/kg; i.p.) was evaluated in the presence of ERa and ERb- selective antagonists (TPBM: 50 Âµg; PHTPP: 50 Âµg, respectively). Results showed that both oral and intraperitoneal administration of AE-PG could produce a significant decrease of immobility, which can be interpreted as an antidepressant-like effect, having a greater effect when administered intraperitoneally. Moreover, PHTPP but not TPBM blocked the antidepressant-like effect produced by EA-PG confirming the participation of the ERb rather than the ERÎ± in the antidepressant-like action. In conclusion, these results suggest that the antidepressant-like effect of EA-PG may be given by estrogenic compounds contained or produced with or even without the need for gut microbiota metabolism and that this effect is mainly mediated by ERb. This project was financed by Conacyt CB-241247.

Speaker

Brenda Valdés-Sustaita Graduate Research Assistant, CINVESTAV

Differential cognitive interference by music stimuli in an unconscious BCI-learning task.

Differential cognitive interference by music stimuli in an unconscious BCI-learning task. S. Vale 1, S. Spoto 1, N. Rosito 1, and J. Rossi III 1. 1 Florida Gulf Coast University, Ft. Myers, FL, USA. Within the field of psychology, cognition, the process of creating knowledge through mental processes, has been studied since the late nineteenth century. One aspect of cognition that has received considerable attention is interference, especially in regard to conscious cognition, the aware completion of mental processes. Interference refers to the tendency for simultaneously occurring perceptual processes to compete for finite cognitive processing capabilities. Many studies have found that the principal components of conscious cognition (e.g., learning and memory) are prone to interference by sensory stimuli. None of the previous studies, however, have addressed or investigated the potential interference of unconscious cognition, or the unaware completion of mental processes. The purpose of the present study was to determine whether an unconscious task would be similarly disrupted by sensory stimuli. Fifty-two undergraduate college students at Florida Gulf Coast University played a scored brain-computer interface (BCI) controlled game while listening to a randomly assigned 4-minute audio stimulus: either pink noise (control group) or the musical track, "Kashmir," with or without vocals (experimental groups). The collected data was analyzed using a one-way ANOVA that yielded a significant effect of auditory stimuli on mean game score, F(2, 49) 6.76, p=.003, eta-squared=0.22. Subsequent post-hoc comparisons using the Tukey HSD test revealed that the mean game score for the pink noise auditory stimulus (M=1823.11, SD=335.72) was significantly different than the “Kashmir” with vocals auditory stimulus (M=1251.12, SD=545.96), p=.002. Also, the mean game score for the “Kashmir” without vocals auditory stimulus (M=1677.82, SD=524.83) was significantly different than the “Kashmir” with vocals auditory stimulus (M=1251.12, SD=545.96), p=.031. The results demonstrated that “Kashmir” with vocals decreased game performance when compared with that of both the pink noise and “Kashmir” without vocals, and that the interference by the vocal track was much more pronounced than for the track without vocals. The findings suggest that unconscious tasks can be disrupted by sensory stimuli and that the complexity of the competing stimuli determine the degree of the interference.

Speaker

Stephen Vale Student Research Director, Florida Gulf Coast University

microRNA regulation related to the protective effects of environmental enrichment against cocaine-seeking behavior

microRNA regulation related to the protective effects of environmental enrichment against cocaine-seeking behaviorAnnika Vannan 1, Gregory L. Powell 1, Michela Dell’Orco 2, Melissa A. Wilson 1,3, Nora I. Perrone-Bizzozero 2, Janet L. Neisewander 11 School of Life Sciences, Arizona State University, Tempe, AZ, USA2 Department of Neurosciences, University of New Mexico Health Sciences Center, Albuquerque, NM, USA3 Center for Evolution and Medicine, Arizona State University, Tempe, AZ, USAMiRNAs (miRNAs) are “master regulators” of gene expression. To investigate miRNAs involved in the incentive motivation for cocaine elicited by exposure to cocaine-associated cues, we conducted NanoString nCounter analyses of miRNA expression in the nucleus accumbens shell of male rats that had been tested for cue reactivity in a previous study. These rats had been trained to self-administer cocaine while living in isolate housing, then during a subsequent 21-day forced abstinence period they either stayed under isolate housing or switched to environmental enrichment (EE), as this EE intervention is known to decrease cocaine seeking. This allowed us to create groups of “high” and “low” cocaine seekers using a median split of cocaine-seeking behavior. We conducted a differential expression analysis across these two groups that identified 33 miRNAs that were differentially altered in the nucleus accumbens shell. Predicted mRNA targets of these miRNAs are implicated in synaptic plasticity and neuronal signaling, and many are known addiction-related genes. Of the 33 differentially expressed miRNAs, 8 were specifically downregulated in the low-seeking group and another set of 8 had expression levels that were significantly correlated with cocaine-seeking behavior. The

findings not only confirm the involvement of previously identified miRNAs (e.g., miR-212, miR-495) but also identified novel miRNAs (e.g., mir-3557, mir-3573) that alter, or are altered by, processes involved in cocaine-seeking behavior. Further research examining the mechanisms involved in these miRNA changes and their effects on signaling may reveal novel therapeutic targets for attenuating drug craving.This work was supported by NIDA grant DA034097.

Speaker

Annika Vannan Graduate Research Assistant, Arizona State University

Cannabidiol as a Potential Preventative Treatment in a Neuregulin-1 Mouse Model of Schizophrenia

Cannabidiol as a potential preventative treatment in a Neuregulin-1 mouse model of schizophrenia Gabriela Visini1, Rose Chesworth1, Tim Karl1,21.School of Medicine, Western Sydney University, Campbelltown, NSW2.Neuroscience Research Australia, Randwick, NSWSchizophrenia is caused by interactions between genes of predisposition and environmental insults. Here we investigated the therapeutic potential of Cannabidiol (CBD) administered in adolescence to protect against the development of schizophrenia-like behaviours, as well as whether CBD could protect against later sensitivity to THC. For this study we used a well-established genetic mouse model of schizophrenia (Nrg1 TM HET mouse). In this study, male Nrg1 mice and wild type (WT) mice were treated with 30 mg/kg of CBD or vehicle intraperitoneally for three weeks during adolescence (PND 35-60). Mice were tested CBD-free in adulthood (5-6 mo) in the open field task, which measures locomotion and anxiety (related to positive symptoms in schizophrenia); social interaction, which measures mouse interactions (relevant to negative symptoms); pre-pulse inhibition (PPI), which measures sensorimotor gating (deficits also found in schizophrenia patients); and fear conditioning, which measures associative learning and memory. Mice were then treated after one week washout with either 3 mg/kg of THC or vehicle, and run in a battery of open field, social interaction, and PPI tests. This study found 30 mg/kg daily treatment with CBD in adolescence facilitated reductions in exploration, locomotion, social interaction and PPI caused by acute adult THC administration in the Nrg1 mouse. Chronic CBD alone also has some effects on this mutant mouse, reducing overall social interaction frequency and affecting PPI. This suggests that chronic CBD can have persistent effects in this mouse model. These data also suggests that the interactions between CBD and THC are complex, and could implicate a relationship where the presence of CBD may strengthen the effects of THC. Brain changes made by CBD during a period of important neural development could impact later THC exposure. We acknowledge Rotary, NHMRC, and WSU for funding.

Speaker

Gabriela Visini PhD Candidate, Western Sydney University

Optogenetic stimulation of the basolateral amygdala-medial entorhinal cortex pathway after spatial training has sex-specific effects on downstream activity-regulated cytoskeletal-associated protein expression

Optogenetic stimulation of the basolateral amygdala-medial entorhinal cortex pathway after spatial training has sex-specific effects on downstream activity-regulated cytoskeletal-associated protein expressionKrista L. Wahlstrom 1, Christa K. McIntyre 4, and Ryan T. LaLumiere 1,2,31 Department of Psychological and Brain Sciences, 2 Iowa Neuroscience Institute, 3 Interdisciplinary Graduate Program in Neuroscience, University of Iowa, Iowa City, IA 52242, 4 School of Behavioral and Brain Sciences, University of Texas-Dallas, Richardson, TX 75080Previous work from our laboratory suggests that projections from the basolateral amygdala (BLA) to the medial entorhinal cortex (mEC) are a critical pathway by which the BLA modulates the consolidation of spatial learning. Posttraining optogenetic stimulation of this pathway enhances

retention of spatial memories. Evidence also indicates that posttraining intra-BLA administration of memory-enhancing drugs increases protein levels of activity-regulated cytoskeletal-associated protein (ARC) in the dorsal hippocampus (DH) and that blocking ARC in the DH impairs spatial memory consolidation. Yet, whether optical manipulations of the BLA-mEC pathway after spatial training also alter ARC in the DH is unknown. To address this question, male and female Sprague-Dawley rats received optogenetic stimulation of the BLA-mEC pathway immediately after spatial training using a Barnes maze and, 45 min later, were sacrificed for ARC analysis. Initial experiments found that spatial training increased ARC levels in the DH of rats above those observed in control rats and rats that underwent a cued-response version of the task. Optogenetic stimulation of the BLA-mEC pathway following spatial training, using parameters effective at enhancing spatial memory consolidation, enhanced ARC protein levels in the DH of male rats without affecting ARC levels in the dorsolateral striatum (DLS) or somatosensory cortex. In contrast, similar optical stimulation decreased ARC protein levels in the DLS of female rats without altering ARC in the DH or somatosensory cortex. Together, the present findings suggest a mechanism by which BLA-mEC stimulation enhances spatial memory consolidation in rats and reveals a possible sex-difference in this mechanism. Acknowledgements: The authors declare no competing financial interests. This work was supported by NIH grants MH118754 (KLW) and MH104384 (RTL and CKM).

Speaker

Krista Wahlstrom PhD Student, University of Iowa

The Well-being Toolbox: comparison of stress reduction techniques in the classroom

The Well-being Toolbox: comparison of stress reduction techniques in the classroom. Walf, Alicia1; Chen, Celia1; Bartlett, Cara1; Antonini, Annabel1; Hahn, Tomie1. 1Rensselaer Polytechnic Institute. Even before the COVID-19 pandemic, self-reporting of stress and anxiety on college campus has been high. Addressing stress and promoting well-being are critical concerns on college campuses across the country. Students studying stress in an upper-level behavioral neuroscience course on our campus, called Stress and the Brain, have noted that the class was helpful to them because they learned about the science of stress and stress-reduction techniques, but also noted that they wish they learned about stress and well-being much earlier in their college careers. To broaden the impact of learning about stress to foster well-being, a first year course was redesigned. In the course, Well-being: Cultivating Curiosity, students learned about the science of stress through lectures and experiential stress reduction techniques, which we referred to as building their 'œWell-being Toolbox.' The term 'œWell-being Toolbox' describes how each person can discover tools, practices and behaviors from many available that can lead to their personal stress-reduction and well-being. In this project, one way stress reduction techniques were compared was by providing students a questionnaire to assess their perspectives on whether approaches used in class 'œhelped develop their well-being self-awareness,' which was reported on a Likert scale. The approaches compared were: use of technology (blood pressure/heart rate cuffs), yoga, Deep ListeningÂ® meditation, creative work, and collaborative work. Students were provided informed consent and the questionnaire at the end of the semester. Of the 38 students enrolled in the class, 28 completed the questionnaire. In asking about whether approaches helped develop their well-being self-awareness, 46.4% agreed or strongly agreed that blood pressure cuffs did, 98.8% for yoga, 60.7% for Deep ListeningÂ®, 75% for creative in-class work, and 71.3% for collaborative in-class work. These data from the first class cohort using this approach suggest benefits for its use. Current research projects on the Well-being Toolbox include its efficacy in a remote learning format. This research project was supported by a grant from Rensselaer Polytechnic Institute's Teaching and Learning Collaboratory.

Speaker

Alicia Walf Senior Lecturer, Rensselaer Polytechnic Institute

Examining Enzyme Replacement Therapy Using A Human Neural Progenitor Cell Model of CLN2 Disease

Examining enzyme replacement therapy using a human neural progenitor cell model of CLN2 disease. Alana M. Williams 1, Aisha Y. Abdool 1, Diane-Marie Brache-Smith 2, James R. Munoz 1. 1 Nova Southeastern University, 2 Miami-Dade College North Campus. Neuronal ceroid lipofuscinosis type 2 (CLN2) is an autosomal recessive, neurodegenerative lysosomal storage disorder due to a deficit of the metabolic enzyme tripeptidyl peptidase (TPP-1). Due to the lack of TPP-1, an accumulation of lysosomal waste leads to cell death. The disease is characterized by language delays, seizures, cognitive and motor decline, blindness and early death. Currently a clinical trial of the experimental treatment BrineuraÂ® (cerilponase alfa) is the only approved treatment for CLN2. The clinical trial involves an intracerebroventricular infusion of recombinant TPP-1. Diffusion models suggest the protein will spread along a concentration gradient through the brain. It is unclear how altered concentrations of TPP-1 will effect ongoing neurogenesis in the subventricular zone. The goal of this study is to examine proliferation, cell cycle kinetics, differentiation, and cell death in human neural stem/progenitor cells (hNPCs) following knockdown, overexpression, or exposure to human recombinant TPP-1. Altered levels of TPP-1 will be assessed using western blot analysis. Proliferation and differentiation will be assessed using immunostaining, fluorescent microscopy, and NIH Image J analysis. Cell cycle kinetics will be assessed using EdU-incorporation assays. Cell death will be assessed using TUNEL assays. We anticipate two 2-way ANOVAs will be used to assess differences between treatment conditions. These results may have implications in clinical trials using intracerebroventricular infusion for enzyme replacement therapies. The original research summarized in the following was supported, in part, by U.S. Department of Education grant award P031C160143 (STEM EnginE). Any opinion, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the respective funding agency.

Speaker

Alana Williams Graduate Student, Nova Southeastern University

Impact of perineuronal net removal on cue-induced reinstatement in cocaine self-administering rats is dependent on memory reactivation parameters.

Impact of perineuronal net removal on cue-induced reinstatement in cocaine self-administering rats is dependent on memory reactivation parameters. Jereme Wingert 1, Angela Gonzalez 1,2, John H. Harkness 1,2, Mae Rose 1, Ryan P. Todd 2, Barbara A. Sorg 1,2. 1 Legacy Research Institute, Portland, OR 97232. 2 Washington State University, Vancouver, WA 98686. Repeated cocaine exposure can lead to the formation of persistent drug memories. Perineuronal nets (PNNs), a specialized form of extracellular matrix involved in neuroplasticity, are modulated by cocaine exposure. The drug-induced increase in PNNs may signify a strengthening of addiction-related pathways as well as a decrease in the ability of the circuitry to return to normal following cessation of drug use. The medial prefrontal cortex (mPFC) is instrumental in cocaine-induced drug-seeking behavior and memory. Here we investigated the impact of removal of PNNs with chondroitinase ABC (Ch-ABC) in the mPFC on cocaine-associated memory reconsolidation. Rats were trained to self-administer cocaine before receiving intracranial Ch-ABC injections either 3 days prior to the reactivation session (pre-reactivation) or 90 min after reactivation (post-reactivation). Memory was reactivated using either a 30 min fixed-ratio 1 (FR1), fixed-ratio 3 (FR3), or a novel variable ratio 5 (VR5) schedule of reinforcement for pre-reactivation animals and on a VR5 schedule for post-reactivation animals. One cohort of animals did not receive any memory reactivation session prior to testing. The next day, lever-pressing behavior was measured for 30 min during extinction and then 30 min during cue-reinstatement conditions. We hypothesized that Ch-ABC given either pre- or post-reactivation would disrupt reconsolidation and attenuate cue-induced lever pressing. Ch-ABC did not affect extinction rate in any conditions; however, Ch-ABC reduced cue reinstatement in the pre-reactivation Ch-ABC cohort when memory was reactivated by the VR5 (but not the FR1, FR3, or No React) session, indicating that memory is reconsolidated only when a novel reactivation session is used. Surprisingly, Ch-ABC given post-reactivation did not attenuate cue-reinstatement. Our results suggest that PNNs in the mPFC may be a target for novel therapies in cocaine addiction, but further exploration of the time-dependent differences in outcome is necessary. Funding: NIH Grant DA040965 & DA033404 and the WSU Alcohol and Drug Abuse Research Program

Speaker

Jereme Wingert Research Assistant, Legacy Research Institute

A tale of two subregions: Olfactory tubercle and nucleus accumbens neurons differentially represent sucrose-seeking and taking

A tale of two subregions: Olfactory tubercle and nucleus accumbens neurons differentially represent sucrose-seeking and taking.Katherine Wright, Daniel WessonDepartment of Pharmacology & Therapeutics, University of Florida, Gainesville, FL, United StatesThe ventral striatum is a group of brain regions that are essential for the regulation of goal-directed, motivated behavior. It is comprised of the nucleus accumbens (NAc) and olfactory tubercle (OT), and they share significant overlap in connectivity, neurochemistry, and cell type composition. Functionally, the NAc has been the focus of intense study into motivated behavior, whereas the OT has been less-well-characterized. However, there is a growing body of evidence that the OT is also a critical hub of the reward circuitry, wherein it flexibly encodes instrumental responding and reward-associative cues. How might these two regions functionally differ during reward-seeking? Self-administration of cocaine directly into the OT is more behaviorally reinforcing than intra-NAc injections, which suggests that reward representation in the OT may be even more pronounced than in the NAc. However, the ways in which neurons in these regions represent reward-seeking and taking is not fully understood. To address this, we recorded simultaneous single unit activity from the NAc and OT in freely-moving mice engaged in three phases of sucrose self-administration: acquisition, where a nose-poke into the active port triggered light + tone presentation and sucrose delivery via the center port; extinction, where no cues or sucrose were delivered; and cue-primed reinstatement, where only cues and not sucrose were returned to the chamber. We found striking interregional differences in the modulation of firing rates of neurons recruited during active port responding and sucrose consumption. Overall, the OT possessed a greater proportion of modulated neurons with increased firing rates whereas the NAc contained a greater proportion of modulated neurons with decreased firing rates. We also observed interregional differences in the duration and magnitude of the activity of these neurons across the sessions that suggests that the OT more robustly represents sucrose-seeking and taking than the NAc. Together, these results uncover unique response profiles among OT and NAc neurons that underscores the heterogeneity in ventral striatum representation of reward-seeking and taking.Funding Acknowledgement: R01DC014443, R01DA049545, R01DA049449 to D.W., and F32DC018452 to K.W.

Speaker

Katherine Wright Postdoctoral fellow, University of Florida

Ventral CA3 projections to the Caudodorsal Lateral Septum Regulate Approach-Avoidance Conflict.

Ventral CA3 projections to the Caudodorsal Lateral Septum Regulate Approach-Avoidance Conflict. Dylan C.M. Yeates 1, Sajeevan Sujanthan 1, Dallas Leavitt 1, Andy C.H. Lee 1,2, Rutsuko Ito 1,3. 1 Department of Psychology (Scarborough), University of Toronto, Toronto, Canada, 2 Rotman Research Institute, Baycrest Centre, Toronto, Canada, 3 Department of Cell and Systems Biology, University of Toronto, Toronto, Canada. The ventral hippocampus is one of the primary regulators of approach-avoidance conflict resolution in rodents. Previous work has shown that the ventral CA3 (vCA3) subfield regulates the avoidance of stimuli that simultaneously predict both positive and negative outcomes, while the ventral CA1 drives approach towards conflict stimuli. We postulated that as one of the few targets of extrinsic CA3 projections, the caudodorsal lateral septum (LScd) and its afferent input from the vCA3 may mediate the avoidance response during approach-avoidance conflict resolution. We therefore transfected the glutamatergic cells of the vCA3 in male Long-Evans rats with either the inhibitory DREADD hM4Di or control EGFP, and cannulated over the LScd for direct drug (CNO) delivery. The animals were trained to associate distinct visuo-tactile cues with either sucrose reward, aversive footshock, or no outcome (neutral) in a Y-

maze. Following successful acquisition, they were run through a 'œconflict test', where they freely explored the combined appetitive-aversive cues and a neutral cued arm. Chemogenetic inhibition of the vCA3-LScd pathway potentiated approach towards the conflict stimulus. Similar effects were observed during feeding initiation in a novel environment, with inhibited animals demonstrating less hesitation to explore familiar food during environmental uncertainty. The same manipulation had no effect on preference for the appetitive or aversive cues individually, nor any effects on food consumption, novelty detection, or locomotion. These findings are consistent with the idea that the vCA3-LScd circuit facilities avoidance during approach-avoidance conflict, and implicate the LScd as a key node in a motivational control network. This work was funded by the Canadian Institutes of Health Research.

Speaker

Dylan Yeates

Microglial depletion impairs synaptic and cognitive function in young and aged rats

Microglial depletion impairs synaptic and cognitive function in young and aged rats
Brittney Yegla1, Jake Boles1, Ashok Kumar1, Thomas Foster1,2
1Department of Neuroscience, McKnight Brain Institute, University of Florida; 2Genetics and Genomics Program, University of Florida, Gainesville, FL
Microglial dysfunction, which generates inflammation, is a characteristic of aging and neurodegeneration. Microglial removal and repopulation pose potential therapeutic options for ameliorating cognitive impairments related to neuroinflammation in aging. To examine the impact of microglial depletion (MD) on hippocampal function, young and aged rats (N=6-7; 6 mo and 22 mo) were treated with PLX3397 (45mg/kg/day), a colony-stimulating factor 1 receptor inhibitor. One cohort of young rats was treated with PLX3397 (21days) to verify drug efficacy in reducing a microglial marker, Iba-1. A second cohort of rats, young and aged, was divided into three groups: MD (PLX3397, 21days); microglial replenished (PLX3397, 21days; no treatment, 14days) and controls. They underwent behavioral testing in a context-object discrimination (COD) task and cued fear conditioning followed by electrophysiology. PLX3397 treatment significantly decreased microglia by 61% ($p<0.001$), without changing morphology. Regardless of age, MD rats were impaired on COD ($p<0.05$), suggesting that microglial loss hinders hippocampal function. For contextual fear memory, aged MD rats froze less than young ($p<0.02$) and age-matched controls ($p=0.06$). During cued fear memory testing, young MD rats overgeneralized their fear response, exhibiting heightened freezing prior to and during cue presentation ($p<0.01$ for both) relative to young controls. Age and treatment interacted for cued extinction ($p=0.02$), whereby young MD rats persisted in overgeneralization ($p<0.01$) and aged rats with replenished microglia froze the least ($p<0.02$). After training, electrophysiological recordings were conducted. Both input-output curves and the slope of the NMDA-specific synaptic response showed an effect of stimulation intensity ($p<0.01$) and treatment ($p<0.01$) due to reduced synaptic responses of MD rats. Overall, MD impaired hippocampal synaptic activity and behavior. These data emphasize the crucial contribution of microglia to synaptic function regardless of age and despite their generation of a pro-inflammatory milieu.
Funding:NIA R37AG036800, R011049711, R01052258, P30-AG028740, and Evelyn F. McKnight Brain Research Foundation

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Speaker

Brittney Yegla Postdoctoral Researcher, University of Florida

A Systematic Review on Olfactory Function in Autism Spectrum Disorder

A Systematic Review on Olfactory Function in Autism Spectrum Disorder.Christina Y. Yin,* Areeba Sharafuddin, Melika Babadi & Florence I. Roullet. McMaster University, Hamilton, Ontario, Canada.
*presentingAutism Spectrum Disorder (ASD) is a developmental disorder characterized by communication

and behavioural atypicalities. Sensory responses in the ASD population have shown to be different compared to the typically developed (TD) population. Behavioural olfactory assessment has been used in the clinical setting for neurological disorders such as Parkinson's disease, Alzheimer's disease, and schizophrenia, suggesting the possibility to use olfaction as part of the battery of diagnostic tools. The aim of this study was to do a qualitative and quantitative review of the olfactory function assessments performed on the ASD population. Articles on olfaction and ASD, published from January 1, 2000, to December 31, 2019, were retrieved from PUBMED, MedLine, and ScienceDirect. The results were organized into seven categories: olfactory identification, olfactory discrimination, olfactory detection threshold, olfactory adaptation, '˜patient' or caregiver questionnaires, psychophysical response to odors, olfactory neuroanatomical and genetic assessments. Risk of bias analysis was completed using the Cochrane risk of bias tool for non-randomized trials. Out of 1896 articles, a total of 32 original papers were included with a total of 3492 participants (1934 ASD; 1558 TD). Altogether, N=1384 ASD participants received '˜patient' or caregiver questionnaires, N=214 underwent olfactory detection threshold tests, N=191 for olfactory identification tests, N= 80 for olfactory adaptation tests, N=65 for olfactory discrimination tests. Of the 32 papers, 11 included olfactory identification tests, 4 included olfactory discrimination tests, 8 included olfactory threshold tests, 1 included olfactory adaptation test, and 11 included '˜patient' or caregiver questionnaires. For olfactory identification, ASD participants performed worse than TD in 63.6% of the studies. For olfactory discrimination in 33.3% of the papers, ASD participants performed atypically as compared to TD. For olfactory threshold, ASD participants performed atypically in 50% of the studies. For olfactory adaptation, no difference was found between the groups. For '˜patient' or caregiver questionnaires, 77% of the papers showed that ASD participants have more sensory problems relating to taste/smell as compared to TD.

Speaker

Christina Yin Student, McMaster University

Sex-specific effects of development on social recognition in rats

Sex-specific effects of development on social recognition in rats. Katie E Yoest, 1, Morgen G Henry, 1, Haley A Velisek, 1, Alexa H Veenema, 1. 1 Michigan State University. The ability to recognize previously encountered conspecifics is crucial for normal social interaction. This social recognition ability is well characterized in adults of both sexes but remains largely unexplored in juveniles. We first determined whether juvenile male and female rats show similar temporal patterns of social recognition to adults, by testing their ability to recognize a previously encountered same-sex stimulus rat 30, 60, or 90 min following initial investigation. Similar to adults, juvenile males showed social recognition 30 and 60 min, but not 120 min, following the initial encounter. Juvenile females, however, did not show social recognition at any time point tested. We then determined at what age during development social recognition ability is established in female rats, by testing females as juveniles, adolescents, young adults, and adults. We found that only young adult and adult females showed social recognition. This developmental difference in social recognition ability was driven by a decrease in the amount of time females investigated the previously encountered (familiar) stimulus. Based on these findings, we hypothesized that social recognition is impaired in juvenile and adolescent females due to a lack of circulating estradiol. To test this, we administered estradiol benzoate (EB) 48 hours prior to testing for social recognition in juvenile female rats. EB treatment induced a preference to investigate the familiar over a novel social stimulus, the opposite behavioral pattern observed in typical rodent social recognition. Also, EB treatment increased investigation of the social stimulus during the initial investigation period. Together, this suggests that additional factors contribute to the lack of social recognition ability in juvenile females. This may include sex and age differences in activation of the bed nucleus of the stria terminalis, a brain area implicated in adult social recognition, which shows social stimulus-induced activation in juvenile females, but not males. These findings provide the first evidence of a development-specific sex difference in social recognition ability. Ongoing work seeks to tease apart the underlying neurobiological mechanisms. Research supported by NSF IOS 1735934 to KEY, NSF DBI 1906523 and NIH R01 MH102456 to AHV.

Speaker

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Immune challenge in mid pregnancy causes sex-specific behavioural changes in adult mouse offspring, reminiscent of neuropsychiatric disorders.

Immune challenge in mid pregnancy causes sex-specific behavioural changes in adult mouse offspring, reminiscent of neuropsychiatric disorders. Yotova, Anna Y. 1,2; Slattery, David A. 1; Reif, Andreas 1; Freudenberg, Florian 1. 1 Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Goethe University Frankfurt, Germany; 2 Faculty of Biosciences, Goethe University Frankfurt, Germany. Aim and Objectives: The purpose of this project was to establish maternal immune activation (MIA) as a prenatal model of psychiatric neurodevelopmental disorders (NDDs) within our institution. Extensive behavioural phenotyping was implemented to investigate abnormalities in the immune-challenged offspring with a distinct focus on sex-specific divergences. The MIA model would then be used to research specific morphological, molecular, and genetic aberrations associated with psychiatric disorders. Methods: MIA was induced on the 9th gestational day via injection of the viral mimetic polyinosinic:polycytidylic acid [0, 2.5, and 5 mg/kg poly(I:C), i.v.] in C57Bl/6J wild-type pregnant dams. The adult offspring (n=83) were examined for exploratory drive, anxiety- and depression-like behaviours, spatial and object memory, social interaction, and sensorimotor gating. Results: Multiple behavioural effects were found in adult offspring of MIA mothers treated with 5 mg/kg poly(I:C). The results revealed novelty-induced hyperactivity and anxiolytic effects in 5 mg/kg treated females. Significant deficits in social interaction and recognition were demonstrated in high concentration offspring of both sexes, reminiscent of social deficits in psychiatric NDDs. Depression-like behaviours manifested for the same group as anhedonia in males (diminished sucrose preference) and decreased nesting behaviour in females. Increased acoustic startle response and a trend towards lower pre-pulse inhibition in 5 mg/kg females suggested slight sensorimotor gating deficits. In contrast to the novelty preference results for the 5 mg/kg offspring, decreased novel arm preference was observed for the 2.5 mg/kg group in a Y-maze, predominately in males. Neither spatial nor object memory deficits were observed in either sex. In conclusion, future studies will combine this model with our genetic models to assess gene x environment interactions. Funding Acknowledgement: This project was supported by the German Research Foundation [project No: 261958349].

Speaker

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Acute effects of cannabis on cognition in aging

Acute effects of cannabis on cognition in aging. Zequeira, Sabrina ; GÃ¼venli, Alara A. ; Bruner, Matthew M. ; Hernandez, Cesar; Deslauriers, Josue F. ; Febo, Marcelo1,2,4 , Bizon, Jennifer L.1,2,4 ; Setlow, Barry1,2,3,4 Departments of Psychiatry1, Neuroscience2, Psychology3, Center for Addiction Research and Education4, University of Florida, Gainesville, FL. Cannabis is the most widely used illicit drug in the United States, and individuals over the age of 65 are the fastest growing demographic of cannabis users. As the number of older adults in the US expected to reach 90 million by 2050 it is imperative to understand the potential cognitive impacts of cannabis consumption in this population. Across species, aged individuals exhibit deficits in cognitive functions supported by the prefrontal cortex (PFC) and the hippocampus. These same cognitive functions are impaired by acute administration of cannabis or THC in young subjects; however, effects in aged subjects have been less well evaluated. The goal of the current study was to use a rat model to determine whether the effects on cognition of acute exposure to cannabis smoke differ between young and aged subjects. Male, fully mature young adult (6 months) and aged (24 months) Fischer 344 x Brown Norway F1 hybrid rats were tested on both a PFC-dependent delayed response working memory task and a hippocampal-dependent trial-unique non-match to location (TUNL) task in touchscreen operant chambers. The delayed response task required rats to remember the location of a visual stimulus over variable delay periods ranging from 0-24 s. The TUNL task required rats to remember the location of a visual stimulus with varying degrees of discriminability from other, distractor stimuli. A semi-randomized, within-subjects experimental design was used such that each rat was exposed to smoke from burning, 0, 3, 5, and 10

cigarettes immediately prior to test sessions in each task. In the delayed response task, acute exposure to cannabis smoke impaired accuracy in young rats but enhanced accuracy in aged rats. In contrast, in the TUNL task, cannabis smoke had no effects on performance in either age group. Considered together, this pattern of results suggests that in aged rats, which exhibit impaired cognitive performance, cannabis smoke can enhance PFC-dependent cognition, but has no effect on hippocampus-dependent cognition. Supported by the McKnight Brain Research Foundation and the McKnight Brain Institute

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Speaker

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Relaxin3 innervation of the parahippocampal region

The relaxin3 innervation of the parahippocampal cortex in the rat. Olucha-Bordonau, Francisco E.1; García-Díaz, Cristina1; Gil Miravet, Isis1; Albert-Gascó, Héctor1,2; Gundlach, Andrew L.3; Castillo–Gómez, Esther1,4; Ros-Bernal, Francisco1 Authors' Affiliations 1 Unidad Predepartamental de Medicina, Universitat Jaume I, Castellón, SPAIN 2 UK Dementia Research Institute, Department of Clinical Neurosciences, University of Cambridge, Hills Road Cambridge, CB2 0AH, UK3 The Florey Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia4 Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain.

The parahippocampal cortex is a set of cortical areas that works as an interplay between other cortical areas and the hippocampus and viceversa. The bidirectional flow of information between the cortex and the hippocampus through the parahippocampal region plays a crucial role in spatial memory and context related learning. The working properties of this system can be modulated from extrinsic connections arising from subcortical n eural centers. One of these centers is the nucleus incertus which is a small group of neurons in the midline of the floor of the IV ventricle in the pontine tegmentum. The neurons of this nucleus produce and release in its projected areas the neuropeptide relaxin3 which has been found to modulate emotional and cognitive learning processes. Previous works have shown that the nucleus strongly projects to the ventral hippocampus and also the parahippocampal cortex but the details of this last projection has not been analyzed in detail. The aim of this work is to study the anatomical distribution of relaxin3 fibers in the different subregions of the parahippocampal cortex and its relationships with the distribution of the RXFP3 relaxin3 receptor. Relaxin3 fibers and also anterogradely labeled fibers from injections in the nucleus incertus preferentially innervate the superficial layers of the medial entorhinal cortex and deep layers of the lateral entorhinal cortex although some fibers also appeared dispersed in the rest of the regions. Labeling was also relevant in the amygdalohippocampal transition area, the endopyriform cortex and deep layers of the perirhinal cortex. However, neurons expressing RXFP3 mainly locate in the superficial layers of the medial and lateral entorhinal cortex. Also only a lower proportion of the relaxin3 positive fibers contain the synaptic marker synaptophysin. Altogether, these results indicate a strong projection from the nucleus incertus to the parahippocampal cortex and open the possibility of non-synaptic delivery of the neuropeptide in the entorhinal cortex to regulate its function. Funding Acknowledgement This research was funded by Fundación Alicia Koplowitz, Spain, grant number 19I436; the Spanish Ministerio de Ciencia, Innovación y Universidades, grant number RTI2018-095698-B-I00); Generalitat Valenciana, grant number GV/2019/088(E.C.-G) and Universitat Jaume I, grant number UJI-B2019-54 (F.E.O.-B.) and UJI-A2017-17 (F.R.-B.)

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