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Valproic acid improves anxiety-like behavior and amphetamine hyper-reactivity in isolation reared trait anxiety rats but reverses the benefits of environmental enrichment.

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Valproic acid (VPA), a deacetylase inhibitor, has been shown to improve functioning in a number of animal models of early life stress (ELS) and mood disorders. The enriched environment (EE) also promotes recovery following ELS, anxiety and depression working at least through epigenetic mechanisms. In the present study, we determined the interaction of VPA with housing environment using 8th generation outbred trait anxiety animals bred along high (HAn) and low anxiety (LAn)-like behavior lines. Animals were housed for 30 days in EE, standard (SE) or isolated environments (IE), tested for anxiety and amphetamine sensitivity, given a 2-week VPA treatment (7 mg/ml) in drinking water, and re-tested on each of the behavioral measures. Results indicate that HAn animals reared in IE and SE showed greater anxiety-like behavior on the elevated plus-maze and open field, and hyper-activity to amphetamine, relative to HAn EE and all LAn groups. VPA decreased the benefits of EE but significantly improved the adverse effects of IE on anxiogenic tests and amphetamine-induced locomotion. Immunohistochemical analysis of corticotropin-releasing hormone (CRH)-immunoreactivity in the central amygdala revealed a significant decrease in CRH-ir in LAn EE-reared rats compared to HAn EE. Collectively, the data suggest benefits of EE and VPA treatment in modulating trait anxiety and isolation rearing behavioral consequences. Moreover, the EE shifts in emotional responding and drug-sensitivity likely work through mechanisms other than regulation of CRH. Keywords: HDAC inhibitor, elevated plus-maze, open field activity, stimulant sensitivity, housing JB was supported by the Undergraduate Research Funds (UMB). STD was funded by the NIMHD (P.I. Celia Moore, Ph.D.) P20 Award Number P20MD002290.

Hippocampal neurogenesis mediates decision making under conflict

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Approach-avoidance conflicts occur when an animal encounters stimuli associated with both positive and negative outcomes. These conflicts are resolved in part by the hippocampus, which acts to modulate the inhibition of prepotent behaviors. Here we examined the behavior of rats lacking neurogenesis in a platform mediated avoidance (PMA) task to determine whether adult-born neurons influence behavior when animals have the option to either avoid footshocks, obtain rewards, or attempt to do both. In the PMA task, animals can choose to avoid each footshock, but avoidance comes at the cost of being unable to lever-press for sucrose rewards. The simultaneous presentation of an auditory conditioned stimulus (CS) that reliably predicts a footshock, and a light cue signaling reward availability, creates an approach-avoidance conflict where the animal must balance threat avoidance with food-seeking behavior. Neurogenesis was eliminated by 8 weeks of treatment with valganciclovir in male transgenic Long Evans rats expressing the herpes simplex virus thymidine kinase (TK) under control of the glial fibrillary acidic protein (GFAP) promoter. Ablation of adult-born neurons was followed by three phases of behavioral training. During the avoidance training phase, animals learned to avoid CS-associated footshocks by stepping onto a small platform. In reward training, pellets were dispensed after each lever press, only while a chamber light was illuminated. During conflict training, auditory and light cues were presented simultaneously. The total time spent on the platform during CS presentation was similar between genotypes throughout avoidance training. Both groups also learned to increase lever pressing in response to the light during reward training. In the conflict phase, however, there was a significant reduction of avoidance behavior in TK animals relative to wild-type controls. The TK group also pressed for rewards at a higher rate and exhibited less freezing behavior in response to the cues. The loss of new neurons was associated with decreased avoidance and increased lever pressing during the presentation of conflicting stimuli, suggesting that neurogenesis plays an important role in regulating approach and avoidance behavior during high-conflict situations. NIH Grant: ZIAMH002784

Developmental exposure to pyrethroid pesticide causes an autism-related phenotype in mouse and prairie vole

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Autism Spectrum Disorder is a cluster of incurable neurodevelopmental disorders with a prevalence of 1 in 54 people. Although autism is commonly thought of as a genetic disorder, up to 50% of autism risk derives from environmental sources. Exposure to pyrethroid pesticides during pregnancy has recently been linked to autism risk by epidemiology studies. Our previous experiments in mouse suggest that developmental exposure to pyrethroid pesticides causes an autism-related phenotype, including decreased vocalizations, repetitive behaviors, learning deficits, and hyperactivity. In this study, we exposed female prairie voles to the EPA reference pyrethroid, deltamethrin, throughout pregnancy and lactation, and tested the resulting offspring for autism-related phenotype. Route of administration mimicked human exposure by being consumed in food at a concentration below the EPA benchmark dose (3 mg/kg every 3 days in peanut butter). One pup per litter was used for each test in a behavioral battery that included ultrasonic vocalizations, marble burying, repetitive behaviors, 24-hour mobility, operant conditioning, partner preference, consoling behavior, and fear conditioning. Biological samples were collected for FOS immunochemistry and omics applications. Results will be discussed in the context of relevance to autism and other developmental disorders. Funding was provided by the National Institute of Environmental Health Sciences to JB (K99ES027869, R00ES027869); the deArce-Koch Memorial Endowment Fund to JB; and a research gift from the Promedica Foundation to the University of Toledo College of Medicine.

Assessment of the neonatal vocalization development in the neurodevelopmental model of schizophrenia.

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Schizophrenia is typically diagnosed during late adolescence or early adulthood, but subtle deficits in communication and sociability are often evident from early infancy. Despite this, socio-communicative deficits are poorly investigated in animals at an early stage of development in schizophrenia-like models. These impairments can be experimentally modeled using rodentsâ€™ ultrasonic vocalizations (USVs). Specifically, USVs emitted by pups separated from mothers/nests serve as a useful tool to reveal reduced attachment with mother.Using a neurodevelopmental model of schizophrenia, based on the prenatal injection of methylazoxymethanol acetate (MAM; 22 mg/kg; embryonic day 17), we assessed early communicative behavior by maternal-separation induced USVs in pups. To study the course of vocal development, pups were recorded at 3-time points: at 6, 9, and 12 postnatal days (PND).The results show that with the development of pups, the acoustic parameters of the USV modify, which results in a more complex and sophisticated signal repertoire. Over time, control pups emit shorter USV with a wider frequency range and increased modulation (PND9 and 12 vs 6). This effect was not observed in MAM rats. MAM male and female pups vocalize comparable to control animals at 6 and 9 PND. However, at 12 PND, MAM rats produced fewer USVs of longer duration than control animals did. Call types distribution did not differ between treatment groups on all experimental days.The present study demonstrates that MAM administration at an early stage of life causes deficits in acoustic communication (reduced number and extended duration of USVs), which may vary depending on the age of the rat pups.This study was supported by the Polish National Science Centre grant NCN 2016/23/B/NZ7/01131.

How a history of avoidance influences generalization and extinction of fear memories.

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Pervasive avoidance is one of the core symptoms of anxiety-related disorders. Therefore, studying its interaction with or causal influence on other fear learning mechanisms involved in the development of maladaptive fear is a valuable approach to improve our understanding the basis of anxiety disorders. Previous studies suggest that a history of controllability over stressors may enhance Pavlovian extinction in humans and rats. However, it is presently unknown exactly how a history of avoidance influences extinction learning. Also, it has been reported that the higher the intensity of the unconditional stimuli (US) or the higher state anxiety during fear learning, the more conditioned fear will generalize. Avoidance responses limit the confrontation with a US and, thus, hinder exposure and habituation to the latter. Therefore, avoidance could increase the aversive value of the US. This possible amplification effect of avoidance on generalization remains untested. Using a platform-mediated avoidance procedure, we performed three experiments where we studied the effect of avoidance acquisition on later extinction of an auditory fear memory. Male rats were divided into avoiders and yoked animals. Avoiders had the possibility to avoid the tone-signaled US by stepping onto a platform (thus giving them some control), while yoked animals (without a platform) received the same tone-shock pairings as the avoider they were yoked to. In a fourth experiment, we assessed the effect of avoidance on generalization of fear memories in male and female rats. We used a similar design as in the preceding experiments but added a generalization phase in which tones of different frequencies were presented. A non-avoider group that received all scheduled tone-shock pairings was also added. In all four experiments we scored time spent on platform, freezing and suppression of bar pressing to evaluate differences between groups and experimental sessions.

Dorsal striatal dopamine dynamics encode the estimation of temporal intervals.

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Temporal control of movement is an essential component of everyday behaviors and relies on cognitive processes including working memory and attention to the passage of time. Patients with Parkinson Disease display deficits in estimating temporal intervals, suggesting that dopamine plays an essential role in interval timing. Depleting or optogenetically manipulating substantia nigra dopamine neurons in rodents disrupts time estimation, indicating that dopamine can directly modulate timing. Additionally, medium spiny projection neurons in the dorsal striatum exhibit time-related ramping activity across temporal intervals. These findings suggest an essential role for dorsal striatal dopamine in interval timing, but exactly how dopamine release regulates temporal estimation is unknown. We investigated this question by recording dorsal striatal dopamine release using fiber photometry and the genetically encoded optical dopamine sensor, dLight, as mice performed an interval timing task. In this task mice are required to â€œswitchâ€• from one response port to another if a reward has not been delivered after a specific interval of time has passed. We found that dLight progressively increased across the temporal interval until reward delivery only in trials where the mouse correctly â€œswitchedâ€• . dLight increased at trial end, when trial cues terminated, but this increase was greater in correct trials with reward delivery. These results suggest that dorsal striatal dopamine release drives striatal projection neuron ramping activity. Ongoing work is exploring how dopamine release relates to striatal neuronal activity as mice perform the interval timing task. These results will provide a mechanistic understanding of how nigrostriatal dopamine regulates time estimation, and more broadly cognitive processing, which will inform development of novel therapeutic interventions for cognitive deficits in Parkinson Disease and other dopamine-related disorders. Funding: 5R01MH116043-04

DNA methylation as a possible epigenetic driver of anxiety-like behavior in an early life adversity model.

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Children who have experienced early life adversity (ELA) via caregiver deprivation are more likely to develop neuropsychiatric disorders like anxiety, a disorder which affects women more than men and demonstrates onset typically during late adolescence and early adulthood. Research in rats has shown similar outcomes: ELA via maternal separation (MS) leads female rats to demonstrate increased anxiety-like behavior earlier compared to males, which is likely driven by earlier corticolimbic development in females. Previous research shows that ELA leads to methylation changes, as well as disrupts parvalbumin (PV) expression in inhibitory interneurons in brain regions associated with anxiety (i.e., prefrontal cortex, basolateral amygdala, bed nucleus stria terminalis). However, these outcomes at the intersection of ELA, anxiety-like behavior, PV expression, and methylation have yet to be fully explored. Here, we characterize the degree to which sex, age, and rearing condition interact to influence behavioral and epigenetic changes following ELA and to identify neural and physiological biomarkers that may predict and/or underlie risk of affective dysfunction later in life. Interestingly, behavioral data from the open field and the elevated zero maze shows age-dependent anxiety-like behavior, with postnatal day (P)45 animals generally exhibiting decreased anxiety-like behavior compared to P25 animals. Here, we also provide immunohistochemistry neural analyses of changes in region-specific 5mc and 5hmc DNA methylation, as well as changes in basal corticosterone levels influenced by the hypothalamic pituitary axis and external stress. These neural and physiological responses may underlie age-related anxiety-like behavior after ELA in a developmentally-dependent manner. Taken together, this work provides insight into potential biomarkers that predict trajectories of anxiety as it relates to adversity. Funded through NIGMS (P20GM103423)

Dopamine projections to the basolateral amygdala mediate the encoding of outcome-specific reward memories.

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To make adaptive decisions, we have to accurately anticipate the potential outcomes (e.g. rewarding events) that might be available. This is facilitated by environmental cues, which we use to retrieve detailed reward memories that enable the predictions and inferences critical for decision making. Although canonically thought to only cache value to predictive cues, emerging evidence suggests ventral tegmental area (VTA) dopamine might also be involved in learning the relationship between a cue and the specific reward it predicts. Our goal here was to explore dopamineâ€™s putative role in such model-based learning and to reveal the projection through which this function is achieved. One candidate projection target is the basolateral amygdala (BLA). We recently demonstrated that BLA principal neurons mediate the encoding of sensory-specific stimulus-reward memories. Using optical imaging and manipulation methods coupled with Pavlovian cue-reward conditioning and the outcome-selective Pavlovian-to-instrumental transfer task, we found VTA dopamine projections to the BLA to be both necessary and sufficient for linking stimuli to the unique rewards they predict, enabling the use of these rich associative memories to inform decision making. Thus, these data reveal a pathway through which dopamine achieves its function in model-based learning and, more broadly, they expose a critical circuit that drives the rich associative learning necessary for adaptive decision making.

Object recognition memory encoding requires hippocampal theta activity

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Theta is the most conspicuous extracellular synchronous oscillation in the mammalian brain. Hippocampal theta relies on an intact medial septum and has been consistently recorded during the acquisition phase of several learning paradigms, suggesting that it is implicated in hippocampus-dependent memory formation. Object recognition memory (ORM) allows animals to identify familiar items and is essential for remembering fact and events. In rats, ORM requires a functioning hippocampus. We found that training adult male Wistar rats in an ORM-inducing learning task involving exposure to two different, but behaviorally equivalent novel objects, increased hippocampal theta power, and that suppressing theta via optogenetic inactivation of the medial septum during training caused anterograde amnesia. Importantly, this amnesic effect was specific to the object the animals were exploring when medial septum suppression was delivered. Taken together, our results indicate that hippocampal theta oscillations are necessary for ORM encoding. Funding Acknowledgement: International Brain Research Organization (IBRO), Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq, Brazil) and Coordenacao de Aperfeicoamento de Pessoal de Nivel Superior (CAPES, Brazil).

Neuronal-specific Diras2 deletion results in distinct behavioural and morphological alterations in mice.

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DIRAS2, a small Ras kinase of unknown function, is associated with adult ADHD. DIRAS2 knockout alters the expression of over 1600 genes in vitro, affecting developmental pathways, and hinting at a role for DIRAS2 in cognitive processes. In this study, we carry out an extensive behavioural battery for ADHD-related traits in mice with neuronal-specific Diras2 deletion. Diras2 involvement in cell growth and developmental pathways motivated us to examine its deletion effects on neuromorphology and target genes' expression profiles in multiple regions of interest (ROIs). Male and female control, heterozygous (HET) and homozygous (KO) Diras2 knockout mice were tested in the open field (OF) and light-dark box (LDB). Females were examined in the auditory fear conditioning (FC) test and the Barnes maze (BM). In males, we evaluated sensorimotor gating using pre-pulse inhibition, and impulsivity and attention in the touchscreen continuous performance test (CPT). Neuronal architecture was analysed via dendritic length, number, and arborisation in Golgi-Cox-stained amygdala and prefrontal cortex of adult males. Expression of Diras1, Diras2, and related targets were examined in females via qPCR in six ROIs. Neuronal-specific Diras2 deletion resulted in significant changes in locomotor activity in HET males and females, albeit in opposite directions, but did not alter anxiety-like behaviour or fear learning. HET males were more impulsive in the touchscreen CPT at baseline conditions, while increased attentional load significantly disrupted the performance in KO males, who also displayed impaired sensorimotor gating. Further, Diras2 downregulation caused region-specific changes in relevant genes' expression and in dendritic architecture in the absence of spine aberrations. Ongoing behavioural, gene expression, and morphological analyses in both sexes and additional brain ROIs would further our understanding of related Diras2 effects and its relevance to psychiatric disorders like ADHD. No external funding sources were used for the project.

The pleasure of absent danger: Neural and emotional responses to the unexpected omission of pain.

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Over the past decade, increasing evidence has pointed to the importance of threat omissions, and the associated violations of threat expectancy for extinction learning and exposure treatment. Yet, important questions remain about how the human brain processes these omissions of expected threat, and how this omission-related neural activity is related to the positive feeling of relief. In order to provide an answer to these questions, 30 healthy volunteers performed the previously validated Expectancy Violation Assessment (EVA) task within an MRI scanner. On each trial, participants were presented with probability and intensity instructions of an upcoming electrical stimulation to the wrist, time-locked by a countdown clock. Most trials, however, did not contain the electrical stimulation and therefore constitute a violation of expectancies. We measured subjective ratings of relief-pleasantness, omission-induced BOLD-responses and changes in skin conductivity during all omitted stimulations. The poster will present the results of this study (currently under analysis). Based on the contemporary fear extinction literature, we predict that unexpected omissions of the electrical stimulation will elicit greater fMRI activations in the Nucleus Accumbens (NAcc), Ventral Tegmental Area (VTA), ventromedial Prefrontal Cortex (vmPFC) and Ventral Putamen (VP); that the magnitude of the signal will increase as a function of instructed probability and instructed intensity (main effect of Probability and Intensity); and that completely predicted outcomes (0% and 100% trials) will elicit equivalent fMRI activation, similar to a reward prediction error signal. Finally, we will apply a cross-validated LASSO-PCR model to identify a multivariate pattern of voxels that can predict self-reported relief-pleasantness. We predict that our ROIs will have an important contribution to the patternâ€™s predictive performance. This project was funded by FWO (National Research Fund Flanders), Belgium (project grant G078920N) awarded to Bram Vervliet.

An in vivo, neuron-specific approach for pairing translational and epigenetic signatures of early-life exercise.

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Exercise alters neuron physiology and molecular function to influence behavior. However, this effect is understudied in the developing brain. Epigenetic modifications induced by early-life experiences play a role in memory function in adulthood; however, the impact of early-life exercise on neural epigenetic mechanisms underlying memory is unexplored. Here we use simultaneous isolation of translating mRNA and nuclear chromatin from a hippocampal neuron-enriched cell population to pair early-life exercise (ELE)-induced changes in gene expression (RNA-Seq) with epigenetic modifications (CUT&RUN-seq). We employ a line of transgenic mice expressing the NuTRAP (Nuclear tagging and Translating Ribosome Affinity Purification) cassette under the Emx1 promoter allowing for neuronal specificity. We developed a technique that combines nuclear isolation using Isolation of Nuclei TAgged in specific Cell Types (INTACT) with Translating Ribosome Affinity Purification (TRAP) methods to determine cell type-specific epigenetic modifications influencing gene expression programs from a population of Emx1 expressing hippocampal neurons. Data from RNA- and CUT&RUN-seq were coupled to evaluate histone modifications influencing the expression of translating mRNA in neurons after ELE. Additionally, we link potential ELE induced epigenetic â€œprimingâ€• with altered transcription after exposure to a learning event. We identify a transcriptional and epigenetic signature of ELE and identify candidate gene-histone modification interactions for future investigations. Our novel method for same-cell population INTACT/TRAP allows for cell-type specific paired transcriptional and epigenomic sequencing. Funding Acknowledgement National Institute of Health: National Institute of Neurological Disorders, Pediatric Epilepsy Research Foundation, Robert Wood Johnson Foundation, UCI Institute for Clinical and Translational Science, Conte Center at UCI

Characterization of parental caregiving behavior of sick offspring in mice.

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Most organisms respond to infection and injury with physiological changes and an array of recovery-focused "sickness behaviors" which include fatigue, appetite loss, and altered social behavior. These behaviors may thus act as social signals allowing for detection and response to sickness. Most investigations of inflammatory-induced sickness focus on social withdrawal and avoidance behaviors. However, there is evidence that sickness can promote familiarity-dependent prosociality. Here we identify how a mouse dam responds with directed caregiving and maternal behaviors toward sick juvenile offspring. Using a multi-camera longitudinal behavioral monitoring system coupled with semi-automated analysis of spontaneous behaviors, we characterized and compared maternal and caregiving behaviors of a mouse dam toward juvenile offspring injected with lipopolysaccharides (LPS) vs. saline controls over the course of 48-hours. Behaviors of interest included pup retrieval, nursing, grooming, nestbuilding, sniffing, huddling, and allo-grooming. Dams were also tested in a social preference assay and time spent in a chamber with LPS- vs. saline-injected offspring and non-offspring was measured. Our results show that dams display increased approach and huddling behavior toward LPS-injected offspring vs. saline controls over the course of 48 hours. Dams also spend more time near LPS-injected offspring than saline-injected offspring in the social preference test. We do not see this effect with non-offspring. Thus, these data indicate that dams exhibit increased caregiving behavior toward sick vs. healthy offspring and display a familiar dependent preference toward sick juveniles. This work was supported by the CTSI TL1 Training Program, NICHD R01-HD088411, and NINDS U19-NS107616.

Prelimbic neuronal ensembles mediate cocaine seeking after acquisition in male and female rats

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Fos-expressing neuronal ensembles are sparsely distributed subsets of neurons that mediate a learned behavioral response. Fos-expressing neuronal ensembles in the infralimbic cortex (IL) are necessary for acquisition and maintenance of operant food- and drug-seeking behaviors. However, the role of prelimbic (PL) neuronal ensembles in the initiation of cocaine-seeking behavior is unknown. Therefore, we sought to elucidate the role of PL neuronal ensembles in initial cocaine seeking. We hypothesize that neuronal ensembles controlling cocaine-seeking form rapidly in the PL during cocaine self-administration. To test this hypothesis, we injected a cocktail of two viruses, a Cre-dependent inhibitory designer receptor exclusively activated by designer drugs (DREADDs), and a Fos-driven CreERT2 molecule into the PL. We then trained rats to lever press for intravenous infusions of cocaine (.75mg/kg) until individual rats met our acquisition criteria of >30 active lever presses and > 70% of total lever responses on the active lever. We then microinfused 4-OH-tamoxifen in the PL to drive recombination within Fos-expressing neurons, resulting in DREADD expression in Fos-expressing neuronal ensembles associated with initial cocaine-seeking behavior. Two weeks later, we injected rats with either vehicle or compound 21(C21) and measured their lever pressing in a non-reinforced cocaine seeking test. Rats in the C21 group decreased active lever pressing on test day, suggesting that Fos expressing ensembles in the PL rapidly form to mediate cocaine-seeking behavior. This viral approach allows us to perform targeted recombination in Fos-expressing neuronal ensembles in rats, opening the possibility for robust behavioral models not available in mouse models.

Preclinical assessment of opioid + non-opioid drug interactions in search for combinations with an improved therapeutic index

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Opioid analgesics are often prescribed for the treatment of moderate or severe pain. However, their use is constrained by unwanted side effects including constipation, respiratory depression, abuse liability and the development of analgesic tolerance. Therefore, there is a need to develop new analgesic treatment methods as an alternative to high dose opioids. One therapeutic approach that can be used to improve the side effect profile of opioids is the administration of a second drug in an opioid-containing mixture. Preclinical studies designed to predict the therapeutic potential of novel opioid-containing drug combinations must rely on quantitative methods to assess their interactive effects. Presented here is an overview of isobolographic analysis along with recent advances in isobolographic theory pertaining to drugs that differ in efficacy and to the statistical analysis of dose-addition. The anatomy of pain processing will also be discussed and the rational development of opioid + GABAergic drug combinations will be presented as an example of application.

Cannabidiolic acid methyl ester (HU-580) in a preclinical schizophrenia mouse model

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Schizophrenia is a heterogenous psychotic disorder that is difficult to treat. Many of the current pharmacological aids come with unpleasant side effects and additional issues with drug adherence and relapse rates. The endocannabinoid system has been recently implicated as a therapeutic system in psychotic illness. While delta-9-tetrahydrocannabinol (THC) has been linked to exacerbating psychotic symptoms, cannabidiol has been shown to provide relief. A newly synthesized analogue of cannabidiolic acid (CBDA) called HU-580 has provided structural stability to CBDA. Reported to be more potent than CBD and CBDA, HU-580 shows pharmacological promise in providing relief for sufferers by antagonizing cannabinoid receptors CB1 and CB2, while agonizing the serotonin-1A receptor. This study focused on investigating the anti-psychotic effects of HU-580 as a therapeutic and preventative treatment in a schizophrenia mouse model. It was hypothesized that the model would induce schizophrenic-like behaviors shown in a battery of behavioral tests that is reversed by acute and chronic HU-580 treatment. A total of 60 C57BL/6 mice were pseudo-randomized into six groups. Mice were given either MK-801 (0.3mg/kg) or saline (i.p. injection) once daily for seven days, and then a single dose of HU-580 or vehicle 30 minutes prior to behavioral tests on days 8, 9, and 10. Mice were then given co-treatment of MK-801 or saline, and vehicle or HU-580 (0.01ug/kg or 0.05ug/kg) once daily for an additional seven days, with follow up behavioral tests conducted. Following acute and sub-chronic modeling, MK-801 induced behavioral deficits consistent with the schizophrenia mouse model. Female mice were more robustly affected by behavioral deficits induced by MK-801 and low dose HU-580 treatment provided therapeutic-like effects in negative and positive symptom behaviors. HU-580 is a new and viable pharmacological aid for treating psychotic symptoms in schizophrenia. Drug tolerance appears to be manageable, and research should continue to measure the affects of this new compound, potentially in humans. Funded by Frederick Banting and Charles Best Canada Graduate Scholarship-Masters (CGS-M)

Basal forebrain cholinergic projections to the basolateral amygdala are necessary to produce durable and extinction-resistant fear memories.

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The importance of glutamate activity in the amygdala for the acquisition and extinction of fear memories is well demonstrated. Recent evidence suggests that cholinergic activity in the basolateral amygdala (BLA), specifically cholinergic efferents from basal forebrain regions, may also be critical. Here, we performed optogenetic silencing of cholinergic BLA projections from the Nucleus Basalis of Meynert (NBM) or the Horizontal diagonal band (HDB) during either fear conditioning or fear extinction. Silencing NBM-BLA projections during conditioning impaired fear recall after extinction and abolished fear renewal. Silencing this pathway during fear extinction had a similar effect on fear recall but spared fear renewal. By contrast, silencing the HDB-BLA pathway during conditioning had no effect on fear recall or renewal. However, silencing this pathway during extinction impaired fear recall and abolished fear renewal. These findings indicate that NBM cholinergic projections regulate fear memories in the BLA at the time of their acquisition and their extinction. By contrast, HDB cholinergic projections primarily regulate fear memories in the BLA during their extinction. We interpret the recall impairments as evidence that the two cholinergic pathways are necessary to guarantee the strength and durability of fear memories. In addition, we propose that these pathways protect fear memories during extinction to ensure their inhibition rather than their erasure. Indeed, we take the loss of renewal after extinction as evidence that the fear memories may have been erased. Taken together, our findings are in line with a growing body of research showing that cholinergic activity in the BLA plays a critical role in regulating the fate of fear memories.This research was supported by an Australian Government Research Training Program (RTP) Scholarship.

Perinatal omega-3 fatty acid supplementation prevents prenatal THC induced pathophenotypes

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Clinical and preclinical studies indicate prenatal cannabis exposure (PCE) pathologically alters fetal brain development and increases vulnerability to neuropsychiatric disorders. However, underlying mechanisms remain unknown. Research in our lab suggests fetal exposure to Δ9-tetrahydrocannabinol (THC) impairs neurodevelopment, in part, through alteration of the lipidomic structure of cortical synaptic membranes. Considerable evidence demonstrates that abnormal cortical synaptic omega-3 (N3) fatty acid lipidomic structure and function may underlie various neuropsychiatric disorders, with evidence suggesting that dietary N3 interventions may prevent or ameliorate symptom profiles. The present study examined if perinatal maternal N3-fatty acid supplementation may prevent the PCE-induced neuropsychiatric pathophenotype. Pregnant Wistar rats were assigned to saline (VEH) or 3mg/kg THC (daily, i.p.) from gestational day (GD) 7 to GD22. Dams were given either N3-enriched or standard diets (control: CT) ad libitum from GD5 to postnatal day (PD) 21 of the progeny. Behavioural (e.g., cognitive and affective capabilities), molecular, in vivo electrophysiological, and cortical lipidomic analyses were conducted to examine the extent of the rescue on PD21, PD35-45, and PD90-120. The behavioural data demonstrates a sex-specific N3-mediated therapeutic effect. PCE N3-treated male and female offspring exhibit significantly improved social, long-term recognition, and spatial working memory. However, only the N3-treated male progeny experience a prevention of the anxiogenic phenotype. The electrophysiological data supports these preventative therapeutic findings, with both male and female progeny exhibiting a mitigation in prefrontal cortical glutamate neuron dysregulation, but female progeny exhibit enduring Hippocampus deficits. These findings demonstrate that dietary interventions aimed at N3-fatty acid normalization may be a promising therapeutic option for cannabis-induced neurodevelopmental pathologies. Funding: Natural Sciences and Engineering Research Council of Canada; CanaQuest Inc.; and MITACS Canada.

Alprazolam exposure during adolescence induces life-long dysregulation of reward sensitivity and second messenger signaling within the VTA-NAc pathway.

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Benzodiazepines are commonly abused concurrently with opioids, resulting in a greater risk for overdose and death. An increase in alprazolam (Xanax; ALP) use/abuse has been reported in adolescents, yet most available neurobiological evidence has been derived from studies using adult models. This study was designed to investigate the behavioral and molecular consequences of ALP exposure during adolescence. Adolescent C57BL/6J male mice (postnatal day [PD] 35) were pretreated with ALP (0, 0.5, 1.0 mg/kg) once daily from PD35-49. Changes in behavioral responsiveness to morphine (2.5 and 5.0 mg/kg), using the conditioned place preference paradigm (CPP) were assessed 24 h (short-term) and one-month (long-term) after cessation of ALP treatment. In a separate experiment, mice were treated with ALP (0.0, 0.5 mg/kg) from PD35-49 and then sacrificed 24 h (short term) or 1-month (long-term) after the last injection to assess levels of extracellular signal regulated kinase1/2 (ERK1/2) protein phosphorylation and its downstream targets (i.e., CREB, AKT) within the ventral tegmental area (VTA) and nucleus accumbens (NAc), a circuit implicated in both drug reward and mood-related disorders. Our results show that ALP-pretreated mice developed a strong preference to the CPP compartment paired with a subthreshold dose (2.5 mg/kg) of morphine (short-term), and this effect was also present in the long-term group. ALP exposure induced short-term increases in ERK1/2 signaling within the VTA-NAc suggesting its repeated exposure enhances the responsiveness of this pathway thus contributing to the enhancement of opioid reward. In the long-term group, we observed increases in CREB and decreases in AKT, while no changes were observed in ERK1/2 within the VTA. Within the NAc, we observed decreases in ERK1/2 and AKT protein phosphorylation. These molecular effects bear resemblance to what is observed during periods of abstinence from opioids, suggesting that ALP exposure during adolescence poses long-lasting detrimental effects that predispose for further drug intake later in life.R01DA046794 (NIDA).

The role of the nucleus accumbens in cocaine memory reconsolidation.

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Addiction is characterized by compulsive drug seeking behaviors. Cravings triggered by cues that were once associated with drug use are a main contributor of relapse. Addictive drugs engage molecular pathways of associate learning, in which recall of a memory is followed by its reconsolidation, strengthening that memory. The reactivation period is a critical time wherein memories are vulnerable to interference. Here we examine the role of the nucleus accumbens (NA), the maintenance of cocaine contextual memories, and explore neuroplasticity involved. Designer receptors exclusively activated by designer drugs (DREADD) were used to inhibit NA neurons. Adult male C57Bl6 mice underwent bilateral intra-NA injections of an inhibitory DREADD followed by cocaine conditioned place preference. After cocaine place preference was established, cocaine memory was reactivated followed immediately by injection of clozapine N-oxide to inhibit NA neurons during reconsolidation. Place preference was re-tested 72 hours and 7 days later. fosTRAP2-Ai14 mouse were used to evaluate plasticity in NA medium spiny neurons (MSN) upon reconsolidation of cocaine memories. Male and female fosTRAP2-Ai14 mice underwent cocaine CPP followed by reactivation of cocaine memory and 4-hydroxytamoxifen injection. Dendritic spine density of fosTRAP cells activated by recall of cocaine context were analyzed. Results show that chemogenetic inhibition of NA neurons following reactivation of cocaine contextual memory, significantly reduced a once established preference for such context. In addition, a significant increase in dendritic spine density in activated NA MSN was found following cocaine memory recall. These findings suggest the NA is important for the reconsolidation of cocaine memories and MSNs exhibit neuroplastic changes upon reconsolidation of such memories. Future directions include chemogenetic inhibition of glutaminergic projections from the ventral hippocampus to the NA to determine if said projection is necessary for the maintenance of cocaine contextual memories. RNAscope of accumbal fosTRAP MSNs will determine if MSNs activated by cocaine context are D1 or D2 receptor expressing. P30DA013429, R01DA043988, T32DA007237.

Social deficits induced by pervasive environmental stressors are prevented by microbial or dopaminergic modulation

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Environmental toxicant exposure, including air pollution, is increasing worldwide. However, toxicant exposures are not equitably distributed. Rather, low-income and minority communities bear the greatest burden, along with higher levels of psychosocial stress. Both air pollution and maternal stress during pregnancy have been linked to neurodevelopmental disorders such as autism, but biological mechanisms and targets for therapeutic intervention remain poorly understood. Using a novel mouse model of combined prenatal exposure to air pollution (diesel exhaust particles, DEP) and maternal stress (MS) in mice, we find that these exposures induce social behavior deficits only in adolescent male offspring, in line with the male bias in autism. Furthermore, using a combination of immunohistochemical and sequencing techniques, we show that these social deficits are accompanied by microglial hyper-ramification and decreased dopaminergic tone within the nucleus accumbens (NAc) in males only. Chemogenetic activation of dopaminergic inputs to the NAc is sufficient to rescue social deficits in male offspring following DEP/MS. In both humans and animal models, the gut microbiome is increasingly recognized as a key regulator of social behavior. Therefore, we also asked whether DEP/MS would shift the composition of the gut microbiome and/or the intestinal epithelium. Indeed, we find that DEP/MS sex-specifically alters the gut microbiome and epithelium of offspring. Finally, we demonstrate that shifting the gut microbiome at birth using a cross-fostering procedure prevents DEP/MS-induced social deficits in male offspring. Together, these data point towards both the dopamine system and gut microbiome as targets for intervention in disorders characterized by social impairments. Funding: This work was supported by R01ES033056 and R01ES025549 to SDB, and by F32ES029912 and K99ES033278 to CJS.

Des-acyl ghrelin reduces alcohol intake and modulates alcohol-related behaviors in rodents.

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There is a growing body of evidence that neuroendocrine mechanisms play a crucial role in the rewarding effects of food and alcohol. Thus, the orexigenic hormone ghrelin has previously been shown to enhance alcohol intake and reward-related behaviours in rodents. However, most of the research up to date has focused on the acylated form of ghrelin, which has been considered to be the biologically active version, even though 80-98 % of total ghrelin in plasma consists of the non-octanoylated form of ghrelin, des-acyl ghrelin (DAG). Intriguingly, recent findings suggest that DAG is metabolically active and decreases food intake and inhibit ghrelin-induced food intake. However, the role of DAG in modulating reward processes and alcohol intake is still unknown. Therefore, we sought to investigate the role of DAG in modulating alcohol intake and alcohol-mediated behaviors in rodents. First, we used the intermittent access model to investigate the effect of both acute and repeated systemic DAG administration on alcohol intake and found that the alcohol intake was decreased in both female and male rats in either paradigm. We then tried to define the effects of repeated DAG treatment in alcohol-consuming rats on monoaminergic neurotransmission by analysing brain tissue samples from several reward-related areas with liquid chromatography. The brain tissue analysis indicated that the ventral tegmental area (VTA) is a target for DAG in male, but not female rats. To further explore the effects of DAG on alcohol reward in male rodents we used locomotor activity tests, conditioned place preference (CPP) and in vivo microdialysis. The findings from these experiments confirmed DAGs effect on neurotransmission in the VTA. Further, DAG successfully attenuated the rewarding properties of alcohol, as measured by alcohol-induced locomotor stimulation, CPP and dopamine release in nucleus accumbens shell. Collectively, our data show that systemic DAG attenuates alcohol intake and alcohol related-behaviors in rodents, in contrast to that of acylated ghrelin, and that this is likely through attenuating mesoaccumbal dopamine signalling.

Neutral sphingomyelinase is a major driver of sex-differences in depression and alcohol-abuse.

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Molecular mechanisms for alcohol abuse and sex-specificity require definition. We investigated the role of neutral sphingomyelinase-2 (NSM) and its coding gene SMPD3 in the self-regulation of emotional state with alcohol. A genetic association analysis in 456,693 volunteers found multiple associations between SMPD3 haplotypes and alcohol consumption and affective state, but also with brain region volume and bone mineralization. Functional analysis of NSM in mice revealed a largely sex-specific, often opposite control of alcohol consumption and how the alcohol regulates depression- and anxiety-like phenotypes. While female mice initially benefit from a protective action of reduced NSM function, males develop an aversive affective state. Both can be eliminated by voluntary alcohol drinking. NSM function controls hippocampal and ventral striatal volume development in female and male mice in opposite ways, which can be reversed by alcohol self-administration. Wide spread enhancement of lipidome sensitivity to alcohol and down-stream adjustment of dopaminergic and serotonergic signalling may underlie this sex-specific morphological and behavioral plasticity. Targeting NSM activity in a sex-specific way may thus be a new goal for future development of alcohol abuse therapies interfering with the use of alcohol for self-management of mental states. ACKNOWLEDGMENT The work of the authors was supported by the German National Science Foundation (Deutsche Forschungsgemeinschaft [DFG]), grant MU 2789/8-2, KO 947/13-3, KO 947/15-2, and TRR265 (Project-ID 402170461), and in part by the Federal Ministry of Education and Research (BMBF) under the e:Med Program (031L0190B and 01KC2004B).

HSV-1 intranasal infection contributes to olfactory behavioral deficits in 5xFAD mice.

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Multiple studies show herpes simplex virus type-1 (HSV-1) contributes to Alzheimerâ€™s disease (AD) progression. HSV-1 increases the risk of dementia and infection shares similar pathological characteristics as those seen in AD, including amyloid accumulation, neuroinflammation, neurodegeneration, and cognitive impairment. In a parallel body of literature, early AD is characterized by smell loss that has been associated with amyloid deposition in the olfactory epithelium (OE) and olfactory bulb (OB), neurodegeneration, and cognitive decline. These studies raise the possibility that HSV-1 disruption of olfactory pathways can accelerate AD. Thus, we hypothesize that HSV-1 infection of the olfactory system triggers smell loss and pathological processes characteristic of early AD. To test this hypothesis, we determined if HSV-1 can infect the olfactory system from the periphery. Mice (5xFAD, AD murine model; C57BL/6) were intranasally inoculated with HSV-1 (10e6 PFU/animal, McKrae strain) or PBS. Five days post-infection (DPI), immunohistochemical analysis revealed more HSV-1 antigen in the OB of the 5XFAD compared to C57BL/6. Surprisingly, C57CL/6 had more HSV-1 antigen in brainstem nuclei compared to 5XFAD, particularly in the trigeminal nuclei. Next, we determined the effects of viral infection on olfactory behavior using a food foraging task. Prior to infection, performance on a food foraging task was assessed in 5xFAD mice and littermate controls. Mice were then intranasally inoculated as above and olfactory deficits (latency to find food compared to pre-infection) were assessed by the food foraging task at 10 and 30 DPI. We found the 5xFAD mice had significantly increased latency to find food at 10 DPI following infection compared to littermate controls; further, these olfactory deficits persisted through 30 DPI. These findings suggest that HSV-1 can accelerate olfactory deficits in vulnerable mice with progressive AD pathology and, by extension, may accelerate progression to clinical dementia in individuals with familial AD.

Chemogenetic inhibition of ventrolateral orbitofrontal cortex produces dissociable effects on stimulus- vs. action-based probabilistic reversal learning

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Reversal learning, impacted in various neuropsychiatric disorders, measures subjects' ability to form flexible associations between stimuli and reward or between spatial responses (actions) and reward. Here we examined the role of the ventrolateral orbitofrontal cortex (OFC) in flexible learning of stimuli and actions using chemogenetic manipulation. Male and female Long-Evans rats (N=20) were prepared with bilateral inhibitory hM4Di DREADDs or eGFP on a CaMKIIa promoter in vlOFC, targeting the major output neurons of this region. Rats first met a discrimination criterion, before being tested on both fully predictive deterministic (100/0) and probabilistic (90/10) reversals, during which they selected a visual stimulus or performed a spatial-based action (i.e., left or right) associated with a sucrose reward by nosepoking a touchscreen. Thirty minutes prior to each reversal session rats were administered clozapine-N-oxide (CNO, 3 mg/kg, i.p.) or vehicle (VEH) solution (3mg/kg, i.p.), using a within-subject, counterbalanced design. Thus, if a rat received CNO on the 1st reversal, it was administered VEH on the 2nd reversal (CNO1-VEH2), or vice versa (VEH1-CNO2). Rats learned the initial stimulus-based task much more slowly than the action-based task (8.4 ± 1.5 vs. 2.4±0.3, sessions to 75%). For deterministic learning, we found that CNO1-VEH2 exhibited a reduced probability of choosing the correct option (GLM: β =0.35, t(168)=2.50, p=.013), fewer rewards collected (GLM: β =73.45, t(168) = 2.03, p=0.04), less adaptive win-stay (p=0.03) and lose-shift (p=0.01) strategies compared to VEH1-CNO2. The same pattern emerged for the transition between deterministic to probabilistic reversals, only for stimulus-based learning. We did not observe the same effect in Action-based reversals. These findings suggest that OFC is critical for encoding a stimulus-reward probability mapping that is later used when updating is needed. We are presently conducting trial-by-trial analyses and comparing vlOFC with other nodes in corticolimbic circuitry (e.g., basolateral amygdala and anterior cingulate cortex). This research was supported by NIDA (RO1 DA047870), UCLA Life Sciences Retention Fund, and NSF GRFP.

M. Goldfarb: Data analysis
T. Ye: Programming of behavioral task
K. Das & J. Perez: Data collection
M. Gomez: Tissue processing and histology
A. Izquierdo (senior author): Funding, conception, design, supervision, data analysis, writing, editing.

Role of acetylcholine release in the prefontal cortex during social interaction

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Previous studies showed that neuronal nicotinic receptors within the prefrontal cortex are necessary for showing adapted social interactions. However, the precise role of acetylcholine (Ach) in this process has never been studied. Aim:The aim of this study is to understand the role of prefrontal cholinergic input in social interaction.MethodsWe targeted opsin expression in cholinergic neurons for activating or inhibiting acetylcholine release in the prefrontal cortex of ChAT-IRES-Cre mice while they are interacting socially in dyads of males. We recorded ultrasonic vocalization (USV) that we showed to be a marker of emotional status and to be promoted by social interaction. ResultOur results show that inhibition of Ach release increased social approach, together with a decrease of USV frequency. By contrast, Ach release decreased social approach, thus changing social hierarchy within the dyad. Moreover, Ach release increased USV frequencies, suggesting an boost of positive emotions. In addition, Ach modulation always induced escape behaviors from the non stimulated mouse. It is, therefore, possible that increased Ach release in the PFC, that trigger higher USV frequency during social approach, may generate an abnormal emotional signal for the social conspecific, which, in turn escapes more frequently social contacts.ConclusionThis study shows that Ach input in the prefrontal cortex modulates social emotional signal, used to establish and maintain social hierarchy.

Genetic disruption of dopamine beta-hydroxylase confers a behavioral syndrome resembling toxoplasmosis in mice.

Daniel Lustberg1, Joyce Liu1, David Weinshenker1. 1 Emory University. Toxoplasma gondii (TG) is associated with neuropsychiatric disorders and is highly prevalent in humans. TG-infected rodents show a behavioral syndrome including reduced aversion to cat odors. Massive suppression of Dbh expression in host organism (reducing NE and decreasing DA) may explain the striking reversal of innate behavior in infected hosts. The locus coeruleus (LC) is the primary source of NE in the brain, projecting extensively within forebrain circuits that govern arousal, stress responses, and motivated behavior. In this study, we examined abnormalities in defensive behaviors and arousal as well as neuronal activity induced by predator odor in Dbh-/- mice and Dbh+/- controls. Dbh-/- and control mice were exposed to a clean cage with a nestlet treated with predator odor (bobcat urine) for 90 min. Immediately after the test, mice were euthanized, and brains were processed for c-fos quantification in the LC and targets implicated in behavioral responses to predator stress. Dbh-/- mice showed high levels of grooming and low levels of burying relative to controls. Controls maintained high levels of arousal throughout the predator odor test, but Dbh-/- mice fell asleep within 90 min. The odor-induced high grooming/low burying phenotype of the Dbh-/- mice was recapitulated in controls pretreated with a DBH inhibitor. Burying was potently suppressed in controls by drugs that reduce NE transmission and signaling, and excessive grooming behavior in Dbh-/- mice was blocked by a DA receptor antagonist. Compared with controls exposed to predator odor, Dbh-/- mice demonstrated increased c-fos induction in the LC and medial amygdala but decreased c-fos in the anterior cingulate cortex, lateral septum, periaqueductal gray, and bed nucleus of the stria terminalis. Moreover, using a novel chemogenetic activity-tagging tool (Fos-TRAP), we captured brain wide networks activated by bobcat exposure (Bob-TRAP) and reactivated them weeks later with CNO in an odorless environment. CNO reactivation of Bob-TRAPed neurons in the odorless context induced robust freezing and increased time spent in corners. In conclusion, Dbh-/- mice may represent a non-infected, monogenetic model of TG infection in rodents, and submit that central NE regulates both arousal and defensive responses to predator odor.

Effects of a KHX-enriched diet on motor behavior and cognition in a MPTP mouse model for Parkinson's disease.

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Parkinson's disease (PD) is a progressive neurological disorder that is increasingly prevalent with age, affecting 2 in 100 people over the age of eighty. PD is characterized by the loss of dopaminergic neurons in the brain, resulting in tremor, slowness of movement, abnormal gait, rigidity and postural instability. PD patients also cope with preceding non-motor symptoms, including cognitive impairment. One of the most widely used PD animal models is the MPTP mouse, which shows clinical PD characteristics such as neurodegeneration, and gait and motor abnormalities. One of the proposed mechanisms underlying Parkinson's disease and MPTP-induced neurotoxicity involves increased reactive oxidative stress (ROS), showing high potential for testing redox modulating compounds such as KHX. Our goal is to investigate efficacy of ROS-redox modulating compound KH176 on behavioral deficits caused by severe damage of the nigrostriatal dopaminergic system due to MPTP administration. Male C57BL/6J mice were assessed for baseline motor behavior using the open field, rotarod, grip strength test, and the Catwalk. After baseline measurements, animals were given either a KHX-supplemented diet or a control diet for the rest of the experiment. One week after diet induction animals were injected twice a week for 5 weeks, with either 15 mg/kg MPTP or vehicle to induce a PD-like phenotype. In addition, all mice received 250 mg/kg probenecid to potentiate the neurotoxicity of MPTP. Three weeks post-treatment animals were re-tested for motor behavior. In addition, contextual fear conditioning was performed to asses cognitive performance. At the end of experiments, animals were sacrificed and the brain collected for molecular and biochemical analysis, including quantification of neurodegeneration and dopamine levels in the nigrostriatal pathway. This work was supported by the Michael J. Fox Foundation (MJFF-003282).

Science communication: Using pop culture to teach children about the brain and behaviour.

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If there's one thing the COVID-19 pandemic has taught us, it is that scientists need to learn how to communicate their work better to the public. Science communication, or "scicomm" as it is colloquially known, can be a powerful tool to make neuroscience research relevant and accessible to a wider audience. This accessibility needs to start in early childhood when children are first learning how science is relevant to them, and that will be the focus of this poster. While neuroscience can be complex, complexity and accessibility are not mutually exclusive. Complex findings can be communicated to children using a variety of strategies, such as age-appropriate pop-culture references, narrative stories, and analogies. We present here one example using popular Avengers characters to teach children about the brain and behaviour. We will use the example of Tony Stark's Iron Man and the Battle of New York to illustrate our body's fight - flight system, as well as acute vs. chronic stress and the impact of each on the human body. We will explain critical facts about the Hypothalamic-Pituitary-Adrenal Axis, the sympathetic–adrenal–medullary axis, and prefrontal cortex as Iron Man fights, and flies, to save New York City. We will also examine Tony Stark's behaviour after the battle from the perspective of chronic stress. While it is unrealistic to explain in detail stress pathways and the underlying mechanisms to children, it is completely possible to break down the key points into digestible pieces. Using pop culture references gives children the ability to use stories and characters they are familiar with to understand and contextualize new information. Plus, they're a lot of fun. There have been many anecdotal stories in the media of late of people who are distrustful of scientists. Involving children in science early might help them see that science is not something "out there," to be feared, and that they, too, have a place in it. Increasing accessibility of research can also help increase the impact of that research, combat and decrease the spread of misinformation, generate community engagement and support, and influence decision-making on both the individual and public level. Funding: DSL - CIHR-Doctoral, IMH award. AD - Canada Research Chair.

Dopamine: A tale of two cities.

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The belief that stimulants, which increase dopamine (DA) levels in the brain, are “cognitive enhancers” and will boost executive functions (EFs) is an example of information mistranslation by popular media. In this poster, we will show one way in which scientists can use analogies to break down complex material for the general public. EFs refer to top-down cognitive processes such as selective attention, self-control, cognitive flexibility, problem-solving, and working memory. They are necessary for navigating our increasingly complex world and depend on several interrelated brain areas, including prefrontal cortex (PFC). DA is an important neurotransmitter in PFC but more DA doesn’t necessarily mean better PFC function since the optimal level of DA in PFC is an intermediate one. Part of the reason for the misunderstanding surrounding stimulants and EFs is that stimulants are often used to treat ADHD (a disorder characterized by lower DA levels in the brain) and depending on the dose has been shown to reduce hyperactivity and improve EFs in those with ADHD. Unfortunately, without fully understanding the complex regulation of DA in the brain and how stimulants work to help cognition and behaviour in ADHD, many people without ADHD have concluded that stimulants will improve their EFs since they improve EFs in those with ADHD. It is easy to see how the erroneous assumption that getting a DA “boost” is beneficial across the board came about. This is one example of research findings being misinterpreted by the public and highlights why better communication about scientific findings to the public is important. In this poster, we will illustrate the transportation systems of two cities called “PFC” and the “Striatum” and how we can use a simple system to teach about DA transporters, the clearance of DA, ADHD, and what stimulants do. Complex science and accessibility do not have to be mutually exclusive. It is our hope that this poster will encourage researchers to reflect on how they can incorporate simple examples when giving interviews, writing articles for a lay audience, and in public engagements to make their work more accessible. Funding: DSL - Canadian Institutes of Health Research-Doctoral award, Institute of Mental Health award. AD – Canada Research Chair.

Encoding of anxiety learning and diazepam treatment by rodent prefrontal cortex and VTA neurons

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Learning that reward motivated actions are associated with the risk of an aversive event is critical for development and expression of anxiety. To model this real-life scenario, we designed a task where instrumental actions taken toward obtaining a reward were probabilistically punished with a mild footshock. We addressed the outstanding questions of whether the ventral tegmental area (VTA) and rodent medial prefrontal cortex (mPFC) adapt to learning of punishment risk in correlation with behavior, and how diazepam influences these neural responses. Fiber photometry was used to measure pan-neural activity in mPFC and VTA in adult male and female rats. This method allowed us to quantify mPFC and VTA neural response to the footshock itself as well as during cue and action encoding epochs which is critical to distinguish how neural responses adapt to receiving versus expecting an aversive experience. We find that selective suppression of male and female behavior developed after 2-3 sessions of task training. This change, or learning, was accompanied by a reduction of phasic neural activity in mPFC and an upward shift in VTA activity, primarily during the peri-action period. Footshock produced a robust activation of neural activity in mPFC and VTA that remained consistent in magnitude after learning. Diazepam did not change the phasic neural response of mPFC or VTA to the footshock nor did it influence mPFC responses to task events. Diazepam did, however, significantly and selectively produce a peri-action ramping response in the VTA and enhanced correlative VTA-mPFC activity. These findings characterize the adaptive neural responses of mPFC and VTA during the learning of anxiogenic contingencies and to the anxiogenic stimulus (footshock) itself. They also identify peri-action ramping of VTA activity as a potential marker for anxiolytic properties of diazepam. This work was supported by NIH grant NIMH -115027

Hippocampal encoding of complementary static and dynamic spatial visual scenes.

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For survival in the real world, animals must internally represent positions of both static (e.g. a nest) and dynamic (e.g. a predator) objects in space. Moreover, animals receive critical spatial information from the part of the environment immediately inaccessible and perhaps not previously explored. The hippocampus is a key structure in spatial cognition, however, there is a lack of understanding of the neural mechanisms that mediate the information processing of both stable and moving inaccessible objectsâ€™ positions. It is also unclear whether spatial representations of static and dynamic objects share mutual features or they belong to separated processing domains. We trained rats to discriminate a particular reward static position of a circle displayed on a distant computer screen and a complementary reward dynamic scene consisted of two circles that approached, but not reached, the same static position. Once the rats mastered the task, we presented them with a set of novel dynamic stimuli to decipher whether they can transfer the acquired knowledge about the previously discriminated static and dynamic spatial scenes into new dynamic spatial scenes. Our data showed that the rats could effectively generalize the objectsâ€™ dynamics and preferred the novel dynamic scene in which two circles approached the familiar reward static position. Next, we implanted the rats with an array of tetrodes and recorded the activity of dorsal hippocampal CA1 neurons during the task. A general linear mixed model showed that the firing rate of individual hippocampal neurons can be influenced by particular positions of a static visual object in our discrimination task. Further analysis is currently underway to examine whether hippocampal neurons encode positional information about complementary static and dynamic object scenes using a similar mechanism. This work was supported by the Ministry of Education, Youth and Sports of the Czech Republic (MSMT) programme OP VVV project FGU MSCA Mobilita IV. CZ.02.2.69/0.0/0.0/20_079/0017164 and Czech Science Foundation (GACR) grant 20-00939S.

ACC neurons respond both during and after response conflict.

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The anterior cingulate cortex (ACC) activates during response conflict (i.e., the simultaneous engagement of incompatible actions, such as going and stopping). The predominant view is that ACC neurons respond only after conflict. This has been studied using the stop signal task in which a cue instructs stopping ongoing movement preparation. However, in this task, there is no observable event demarcating when response conflict occurs on each trial. Thus, it is unclear when and how ACC activity changes during response conflict. We used head-fixed rats on a treadmill to observe response conflict with precise timing. Rats were trained to run after a Go stimulus and to remain immobile after a NoGo stimulus. If they released a pre-potent running response on a NoGo trial, sometimes they still correctly responded by stopping before crossing a distance threshold. These â€œnear-mistakeâ€• movements were characterized by running and reaching a peak velocity, followed by slowing and then immobility. The magnitude of peak velocity is a proxy for the degree of conflict on each trial because stopping higher velocity running requires a greater conflicting stopping response. The time of peak velocity indicates when conflict is maximal on each trial. We assessed firing rate of 478 ACC single units from -0.4 to 1.4 s around peak velocity. Trials were divided into tertiles of peak velocity representing none-to-low, medium or large conflict. 209 units significantly scaled firing rate with peak velocity during near-mistakes (31% correlated positively and 18% negatively), but did not do so during running to a Go stimulus when there is no conflict. Using demixed PCA, we show that specific components of the population activity (simultaneously recorded units) scale with conflict. Scaling was detected for single units and population activity as early as 0.4 s before and 1.4 s after peak velocity. Our findings provide evidence for ACC single neuron and population activity correlating with response conflict magnitude. In contrast to current thinking that ACC only monitors past performance, we show that ACC neurons respond during conflict resolution. Funded by Acad. of Finland, Juselius Foundation, Uni. Helsinki, MPI-Biol. Cyb., Joachim Herz Foundation, AvH Foundation.

What dads do is important too: Paternal preconception drug effects on neurobehavioral development of their offspring

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The adverse effects of maternal drug exposure during gestation on the neurobehavioral development of offspring is well documented. However, paternal drug exposure before conception is less well studied. Originally, it had been thought that effects of paternal drug exposures would be minimal because they would not entail direct actions on the developing fetal brain, but it is now clear that these treatments can change sperm epigenetics to provide a mechanism for paternal contributions prior to conception. In rat models, we found that paternal preconception treatment with tetrahydrocannabinol (THC) evoked significant behavioral anomalies in the offspring, including locomotor hyperactivity, decreased novel object recognition and attentional impairment. Interestingly, although paternal cannabis extract exposure likewise elicited neurobehavioral consequences, these were distinct from those of THC, implying contributions from other components in cannabis, differences that were confirmed by examining synaptic mechanisms for the two types of exposures. We found adverse effects on cholinergic and dopaminergic function that were distinct for THC vs. cannabis. As a likely underlying cause of these effects, there were epigenetic changes in paternal sperm and in the brains of the offspring, specifically targeting genes known to be involved in brain development, associated with disorders such as autism. Notably, some of the epigenetic changes persisted even after 8 drug-free weeks prior to mating, and neurobehavioral deficits were still found in the offspring; this points to persistent effects on spermatogonia. Turning to tobacco, as a comparison to cannabis, we found that paternal nicotine exposure prior to mating likewise evoked neurobehavioral deficits in the offspring, again involving epigenetic changes in the sperm. Taken together, our studies demonstrate that paternal preconception drug exposure can cause persisting impairments in neurobehavioral function of their offspring. Supported by the John Templeton Foundation (60564 and 60957), National Institute of Environmental Health Sciences (ES022831) and the US-Environmental Protection Agency (RD83543701).

The basolateral amygdala to nucleus accumbens shell pathway encodes, but doesn’t retrieve, outcome-specific predictions to guide choice between actions

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Outcome-specific predictions drive the accumulation of delta-opioid receptors (DOPR) on the membrane of cholinergic interneurons (CINs) in the nucleus accumbens shell (NAc-S) to promote choice between actions. Here, we aimed to provide decisive evidence that outcome-specific predictions control DOPR accumulation and to establish whether this control is mediated by projections from the basolateral amygdala (BLA) to the NAc-S. We confirmed that outcome-specific predictions drive DOPR accumulation on NAc-S CINs and found that this accumulation can be removed by systemic administration of the DOPR agonist SNC80. Remarkably, DOPR accumulation was reinstated by a single session retraining the outcome-specific predictions, underscoring the causal relationship between these predictions and DOPR expression. To establish whether this relationship relies on the BLA to NAc-S pathway, we optically silenced this pathway during outcome-specific predictive learning and assessed the impact on subsequent choice between actions. BLA to NAc-S silencing abolished the traditional influence of outcome-specific predictions on choice between actions. In another experiment, we found that the same silencing had no effect when it was conducted at the time of choice. Taken together, these findings indicate that the BLA encodes outcome-specific predictions and drive DOPR accumulation on NAc-S CINs to guide choice between actions. However, they also show that the BLA does not control how this accumulation is then used to guide choice, suggesting that other brain regions may oversee this control. The research reported in this current project is supported by the UNSW Scientia PhD Scholarship.

Acute effects of cannabis on cognition in aging.

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Older adults are the fastest-growing group of cannabis users in the US. Cognitive functions supported by the prefrontal cortex (PFC) and hippocampus are impaired in aged compared to young subjects. These aspects of cognition are also impaired by acute administration of cannabis in young subjects; however, effects in aged subjects have received less evaluation. The goal of this study was to determine whether the cognitive effects of acute cannabis smoke exposure differ between young and aged rats. Male and female young adult (6 mo.) and aged (24 mo.) Fischer 344 x Brown Norway F1 hybrid rats were tested on a PFC-dependent delayed response working memory task (which required remembering the location of a visual stimulus over variable delay periods ranging from 0-24 s) and a hippocampus-dependent trial-unique non-match to location (TUNL) task (which required remembering the location of a visual stimulus with varying degrees of discriminability from other, distractor stimuli in the absence of delays). A randomized, within-subjects design was used such that each rat was exposed to smoke from burning 0, 3, and 5 cannabis cigarettes immediately prior to test sessions in each task. Initial data suggest that in the delayed response task, acute exposure to cannabis smoke in males impaired accuracy in young rats but enhanced accuracy in aged rats, whereas cannabis smoke tended to impair performance in females of both ages. In the TUNL task, cannabis smoke had no effect in male rats, but had opposite effects in female rats (impairing accuracy in young but enhancing in aged). Together, these results suggest that the cognitive consequences of acute cannabis exposure differ as a function of age, and that these differences are moderated by both sex and the form of cognition evaluated. Supported by NIH RF1AG072714 and T32AG061892, Florida Department of Health 21A11, and the McKnight Brain Research Foundation

Differential effects of social, physical, and cognitive stimulation in APPNL-G-F mice

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Our elderly population often falls victim to social isolation, especially during the COVID-19 pandemic. This is particularly worrisome given the negative impact of social isolation on various age-related disorders, such as Alzheimer's disease (AD). The present preclinical study examined the putative therapeutic effects of 3 months of cognitive (CS), physical (PS) or social stimulation (SS) in 14 APPNL-G-F mice (7 females, 7 males), a novel mouse model of AD pathology, and 16 wild-type mice (C57BL/6JRJ; 9 females, 7 males) that had been exposed to 4 weeks of social isolation. CS was provided in a basic Marlau cage protocol (with labyrinth), whereas PS and CS were induced by adding a running wheel to the cage, or by housing in larger social groups, respectively. Each intervention was evaluated by a large battery of tests of anxiety (elevated plus maze), activity (cage activity, open field test), sociability/social memory (SPSN test), and memory (passive avoidance, novel object recognition test). Moreover, a separate cohort of female wild-type mice (N = 12) were subjected to the same interventions (4 per group), and injected with 5-bromo-2'-deoxyrubidine (100mg/kg, i.p.) to assess adult hippocampal neurogenesis. Immunohistochemical co-staining of dentate gyrus neurons with markers of mature (NeuN) and immature (DCX) cells was used to determine the proportion of new-born neurons per intervention group. Briefly, SS marginally improved passive avoidance memory in APPNL-G-F mice, and enhanced adult hippocampal neurogenesis compared to the PS and CS groups. CS ameliorated neophobic and hypoactive behaviors in APPNL-G-F mice. Our results provide a first indication that each intervention type has a different effect on AD pathology. This project was funded by FWO-Vlaanderen.

Nicotinic receptor activity in the nucleus accumbens differentially alters sign-tracking during a contingency change and overtraining.

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Reward predictive cues can acquire their own motivational value, leading to cue-triggered Pavlovian conditioned approach (i.e, sign-tracking. In dynamic environments, persistent responding to cues that no longer predict reward is maladaptive; thus, animals must learn to flexibly respond to changes in the environment. While there is strong evidence that animals adjust their sign-tracking behavior after introduction of an omission schedule, where deflection of a lever-cue cancels delivery of the reward, the neural mechanisms underlying this flexibility remain elusive. One area of intrigue is the nucleus accumbens core (NAcC), whose role in governing sign-tracking behavior has been extensively studied. Within the NAcC, there is a small population of cholinergic interneurons that have historically received little attention despite their modulatory power over dopaminergic input that is essential for the maintenance of motivated behaviors. Recently, these cells have been studied with respect to other flexible behaviors, but it is unknown what role cholinergic transmission plays in the regulation of sign-tracking behavior during the omission schedule. To address this, I evaluated the role of local cholinergic transmission in the NAc following acqusition of sign-tracking training behavior during two conditions: during an omission schedule or during sign-tracking overtraining. Nicotinic receptors (nAChR) in NAcC were inhibited via infusion of mecamylamine prior to each of the first five sessions of omission or overtraining. In the omission schedule, nAChR blockade reduced the rate at which rats altered their sign-tracking responses to meet the new contingency change in comparison to controls; although nAChR inhibition did not entirely prevent acquisition of the adjusted responses and induced increases in reward port entries. Blockade of nAChRs during overtraining did not significantly change sign-tracking responses, suggesting that the effects of the drug may be specific to the omission schedule. Altogether, these results indicate that activity at NAcC nicotinic receptors may regulate behavioral flexibility in response to new information about reward-predictive cues. Funding: NSF IOS 1557987 (KSS); NIH 1R01DA044199 (KSS)

Driving is a no (new) brainer: The impact of adult neurogenesis on cognitive learning in male Long-Evans rats.

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Although adult neurogenesis (AN) has been associated with several cognitive and emotional functions, questions about the specific nature of AN in adaptive neurological processes remain unanswered. The current study investigated the influence of AN on attention and learning in a long-term cognitive training task [i.e., learning to drive a rodent operated vehicle (ROV)]. Transgenic Long Evans rats expressing a viral gene under the GFAP promoter and treated with an anti-viral drug to stop neurogenesis (TK) were used as an AN-deficient group (n=7) that was compared to wild type (WT) rats treated with the same drug (n=8). Habituation and training occurred 5 days/wk for 7 weeks for up to 5 min/day. Daily performance was recorded (e.g., successful trials, progress toward final goal). Results indicated TK rats achieved the criteria for successful driving in fewer sessions than WT rats (p=.044). Further, stress hormones (corticosterone, DHEA) assessed before, during, and after driving training revealed the TK rats had lower DHEA fecal metabolites (p=.015) indicating lower emotional resilience. Following training, rats were assessed in a pattern separation task to investigate attention and memory. During the habituation trial WT rats exhibited more frequent freeze responses in the novel environment (p=.009). During initial introduction of pattern stimuli, TK ratsâ€™ behavior suggested enhanced exploration [i.e., nonsignificant trends for greater distance traveled (p=.054) and higher movement velocity (p=.055) as well as increased visits to the center zone (p=.026)]. During the novel pattern trial, TK rats exhibited longer latency to approach the novel pattern stimulus (p=.023), indicating slower novel pattern recognition. Doublecortin staining confirmed lack of AN in TK animals. Prior to perfusions, animals were placed in proximity to the ROV to assess neural responses to the car in the absence of reward via c-fos immunoreactivity in the nucleus accumbens. This analysis is ongoing, as is IHC assessment of the neuroplasticity marker BDNF in the hippocampus and amygdala. These findings suggest the ROV task provides new opportunity to investigate optimal neural contexts necessary for effective cognitive training.

Free choice high-fat high-sugar diet during adolescence or adulthood alters feeding behaviours

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Obesity is a major problem in modern society and is driven by maladaptive dietary habits including overconsumption of foods high in fat and sugar. These highly palatable foods can highjack the homeostatic regulation of feeding. Increasingly, obesity in adolescents specifically is becoming an emerging concern. Early life stages such as childhood and adolescence are critical developmental periods with major neurobiological, behavioural and psychological changes. This brain immaturity also constitutes a vulnerability window to external insults. Access to either high-fat or high-sugar diets during adolescence alters brain processes, including motivation, memory and feeding. However, animal models exposing mice or rats to just high fat or just high sugar diets do not capture the diversity of our human diet. Humans have complex food environments with many different sources of nutrients (carbohydrate, fat, protein) and can choose which foods or drinks to consume. To better model this, we gave mice several food/drink options within their home cages. We investigated how a free choice high-fat/high-sugar diet starting either at adolescence or adulthood affects feeding and reward-related behaviour. Adolescent (post-natal day 28) or Adult (> post-natal day 70) mice were given free and continuous access to a combination of standard chow pellets, high-fat pellets (60% fat), water and 5% sucrose solution. Control animals were given standard chow and two bottles of water. Adolescent and adult mice exposed to this diet showed increased body weight; they had a preference for high-fat food and sucrose solution, which led to increased energy intake. After 8 weeks of diet (either starting in adolescence or adulthood), high-fat/high-sugar mice had a clear deficit in food-seeking measured with instrumental behaviour and progressive ratio tasks. They had reduced lever pressing for food rewards, and a decreased interest in those rewards (they consume less). We also report decreased preference for different concentrations of saccharin suggesting changes to their sensitivity to rewards. We are currently investigating whether limited exposure to these diet choices just during adolescence (post-natal day 28 to 50) will have the same impact on feeding and reward-related behaviours.

The sympathetic nervous system in cocaine use disorder.

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Cocaine use disorder (CUD) is a serious public health problem, characterized by severe consequences in health, well-being, and functionality. While most research into CUD focusses on the brain, cocaine has deleterious effects on the cardiovascular system as well, which have received far less attention. The cardiovascular consequences are difficult to detect because individuals typically remain asymptomatic until an acute cardiac event such as a myocardial infarction or an arrhythmia, which can lead to mortality. As such, there is a great need for easy screening procedures to monitor cardiac problems in this population to enable early intervention. Here we assessed heart rate variability (HRV), a measure of the fluctuations in autonomic input to the heart, in 78 patients with CUD and 56 healthy control participants. All participants underwent a five-minute electrocardiogram recording, measured supine and standing. For the time domain analysis, HRV measures did not reveal any difference between the two groups when assessed in either position. For the frequency domain, there were no group differences when assessed supine, however the LF:HF ratio measure was significantly different between the groups when participants were asked to stand up. CUD patients showed a blunted response, indicating reduced sympathetic activity in adjusting to the challenge of standing up. Chronic sympathetic nervous system activation, due to cocaine use, may be leading to the desensitization of adrenergic receptors, which could explain this diminished response. More longitudinal work on cocaine and HRV is necessary to determine the predictive value of the LF:HF ratio as a metric for this population. Our data shows an opportunity for new collaborations between the fields of physiology, psychiatry, and neuroscience.

Prefrontal cortex mitochondrial dysfunction links gestational stress and depressive-like behavior in postpartum rats

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Postpartum depression (PPD) is a major psychiatric complication of childbirth, affecting up to 20% of mothers, yet remains understudied. Many of the proposed mechanisms underlying PPD pathology share a link with mitochondria â€“ dynamic organelles crucial for numerous cellular processes. The brain relies on mitochondrial energy production to function properly, and stress, a major risk factor for PPD, amplifies brain energy demands. In turn, brain mitochondrial function is also affected by stress and linked to anxiety-like and social behaviors. Consequently, failure to properly adapt to the demands of stress could increase the risk for psychiatric illness. Considering the importance of mitochondria in regulating brain function and behavior, we hypothesized a role for mitochondrial dysfunction in association with behavioral changes in a chronic stress-induced rat model of PPD. Adult female Wistar rats were separated into nulliparous: controls (C), and stressed (S), and primiparous: controls (P), and stressed (P+S) groups. P+S and S groups were exposed to chronic mild unpredictable stress for a period of 10 days corresponding to the P+S late gestational period. Anhedonia and stress-coping behaviors measured in the early postpartum period were increased in P+S rats, while anxiety-like behavior was unaffected. On postpartum day 11, ex vivo mitochondrial function measured in prefrontal cortex (PFC) was decreased by gestational stress, while nucleus accumbens respiration was unaffected. Pro-inflammatory cytokines in plasma and PFC were increased in P+S and S rats. Interestingly, latency to become immobile in the FST positively correlated with respiration, while respiration negatively correlated with TNFÎ± levels in the PFC of P+S dams. Our findings point to a role for PFC mitochondrial respiration in PPD-like behaviors following gestational stress.Funding Acknowledgement: This work was funded by an internal ASPIRE I grant, and Dept of Veterans Affairs VISN7 RDA to FH and a UofSC Magellan Apprentice and mini-Grants to BR.

Cellular and neurochemical mechanisms of the cannabidiol antipsychotic-like effect: involvement of 5-HT1A and CB2 receptors

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Schizophrenia is a complex and disabling disorder. Cannabidiol (CBD) induces antipsychotic-like effects by still unclear mechanisms. The present study assessed whether repeated treatment (30mg/kg/day, 7 days) with CBD would reverse the behavioural and molecular changes caused by chronic administration (0.5 mg/kg i.p., twice a day, 14 days) of the glutamate NMDA receptor antagonist MK-801to male C57BL/6J mice. We also investigated if these effects involve the activation of 5-HT1A and CB2 receptors by pre-treating the mice with WAY100635 or AM630, 5-HT1A and CB2 receptor antagonists, respectively. At the end of the treatment period, the animals were submitted to the short-term (NOS) and long-term (NOL) novel object recognition test. Changes in the brain expression of the Iba-1, parvalbumin (PV) and Wisteria Floribunda agglutinin (WFA) proteins were also evaluated. CBD attenuated the impairments in the NOS and NOL tests induced by MK-801. This effect was blocked by WAY100635 but not by AM630. In addition, MK-801 increased microglial activation and decreased the number of PV+ cells and the intensity of WFA labelling co-located with PV+ (WFA/PV+) in the pre-limbic area of the prefrontal cortex (PFC), CA1 ventral area and ventral subiculum of the hippocampus. CBD reduced these MK-801-induced neuroplastic changes, an effect that was attenuated by WAY100635 and AM630. We also investigated whether CBD would, through a 5-HT1A mechanism, increase extracellular concentrations of dopamine (DA) in the PFC using the microdialysis technique. Systemic and local administration of CBD significantly increased extracellular DA concentrations at the PFC. The systemic effect was blocked by previous treatment with WAY100635. Together, these data reinforce the proposal that CBD has antipsychotic properties through a mechanism mediated by 5-HT1A and CB2 receptors.Funding Acknowledgement: CAPES, CNPq, IBRO, Cannalatan and FAPESP

Effects of chemogenetic manipulation of the ventral hippocampus to nucleus accumbens pathway on sign- and goal-tracking behaviors

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Cues in the environment can gain motivational value when paired with rewarding stimuli. This relationship becomes maladaptive when cues are associated with addictive substances. Pavlovian conditioned approach (PCA) training is used to assess individual variation in the attribution of incentive value to reward cues, which is linked to a proclivity towards addiction and relapse. When the presentation of a lever precedes a food reward, â€˜goal-trackingâ€™ rats (GT) direct their behavior away from the cue and towards the food reward, suggesting that the lever is solely a predictor. Meanwhile, â€˜sign-trackingâ€™ rats (ST) approach the lever, indicating that they are attributing incentive salience to the cue itself, which makes them prone to addiction-like behaviors. Despite the apparent relevance to addiction and other psychopathologies, the underlying neurocircuitry remains poorly understood. Glutamatergic transmission to the nucleus accumbens (NAc) is important for sign-tracking behaviors in rats. Additionally, our previous work has found that lesions of the ventral hippocampus (vHPC), which densely innervates the NAc, lead to decreases in sign-tracking. We therefor hypothesized that the vHPC-NAc glutamatergic projection may influence sign- and goal-tracking. To test the effects of this pathway, we used an in-vivo dual vector approach to inject Cre recombinase into the NAc and either an inhibitory Gi-coupled, or excitatory Gq-coupled, DREADD into the vHPC. Rats then received injections of CNO or vehicle before PCA training for six days to analyze effects of pathway manipulation on behavior acquisition. On the 7th day, rats received a crossover injection with the other treatment (CNO or vehicle) to examine effects on behavior expression. Our results show that chronic inhibition of the pathway does not seem to affect sign- and goal-tracking behaviors, while ceasing chronic inhibition, through crossover treatment, leads to decreased sign-tracking behaviors in sign-trackers. Chronic excitation revealed a sex difference in sign-tracking, with male rats showing decreased sign-tracking. These results indicate that the vHPC-NAc projection may modulate the acquisition and expression of sign-tracking behaviors in a sex-dependent manner.NIDA R01 DA044960

Stress-related neurochemical modulation of reward-related risky decision-making and response inhibition involving punishment.

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Decision-making involving choice between different actions that may yield rewards associated with costs or punishments is mediated by dopamine circuits. Stressors can differentially alter how these systems regulate action-selection depending on the type of costs being evaluated. We have shown acute restraint stress does not alter preference for larger/uncertain rewards vs smaller/certain ones, but markedly shifts preference away from more effortful rewards. However, how stress may modulate decisions where rewards are linked to punishment has yet to be fully explored. Here we examined how acute restraint and pharmacological stress influenced action-selection on two tasks involving reward-seeking under risk of punishment in male and female rats. One series of experiments utilised a risky decision-making task involving choice between a small/safe lever always delivering one reward pellet and a large/risky option delivering three pellets but that could also deliver foot shock with an increasing probability across blocks of trials (0, 25, 50, 75, 100%). In well-trained rats, one-hour restraint enhanced punishment sensitivity, markedly reducing preference for the shock-associated reward comparably between males and females. In contrast, the Î±-2 noradrenergic antagonist yohimbine had minimal effects on choice. In a second study a go/no-go task assessed ability to inhibit approach towards a readily available reward associated with punishment. Here, a food pellet was delivered in a cup, and on 30/60 trials the rat merely had to approach and retrieve reward. On the other 30 trials, a 12-s visual/auditory warning cue signaled food retrieval also delivered foot shock and that approach must be withheld until cue termination. Restraint and yohimbine had comparable effects: males were more impulsive on test day but females markedly less the day after. These findings suggest acute restraint enhances the effects of punishment on choice between different rewards while differentially altering sensitivity to punishment-associated cues in males and females. The mechanisms underlying this effect may relate to the increased risk aversion observed in individuals with depression. This study was funded by CIHR.

The impact of pubertal stress on maternal memory formation.

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Early life stress has been shown to have a negative impact on adaptive and efficacious parenting in humans. Previous studies have established that induced maternal behavior by exposure in virgin mice is enduring. We have previously shown that stress during puberty alters the hypothalamic-pituitary-adrenal (HPA) stress axis response in adult females only during pregnancy and postpartum. Specifically, pubertal adversity led to a blunted HPA response during pregnancy, which was associated with increased postnatal depression scores in humans.We also observed mild alterations of pup-directed behaviors in pubertally stressed dams. It is possible that pubertal stress creates a disorganization of maternal responsiveness and an increased vulnerability to affective dysfunction.We hypothesized that virgin females who experienced pubertal stress would have a deficit in the ability to form maternal memory in adulthood. Females were exposed to chronic variable stress from postnatal day (PN) 21-34, during which they received one stressor (olfactory, tactile, or auditory) per day for two hours each day. In adulthood, virgin females were tested for response to novel pups in a variety of contexts. First there were four periods of exposure to unfamiliar pups and then a subsequent pup retrieval task in a maze. The behavioral testing was repeated two weeks later with complete separation of females and pups in the interim. Initial behavioral analyses indicated that maternal behavior was harder to ingrain in pubertally stressed females, such that they require more exposures to novel pups to show evidence of maternal behavior. Additionally, the group that experienced pubertal stress but not maternal exposure showed no capacity for pup retrieval, supporting the hypothesis that pubertal stress negatively impacted maternal behavior. Ongoing molecular studies will examine a potential role for the medial preoptic area and paraventricular nucleus of the hypothalamus. Stress during puberty could have a lifelong impact on continual parental responding and stimulation, which is supported by maternal memory. These results will provide novel insight into the impact of adversity during puberty on lifelong risk for altered maternal behavior. Supported by: NICHD grant HD091376

Dysphoric Side Effects of SR141716 (Rimonabant) were Likely Predictable from Preclinical Animal Models.

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AIM: SR141716 (also known as rimonabant; trade names Acomplia, Zimulti) is an inverse agonist at the cannabinoid CB1 receptor, with anorectic anti-obesity properties. It was approved in Europe for the clinical management of obesity in 2006, but withdrawn worldwide in 2008 due to serious psychiatric side effects. OBJECTIVE: To show that these side effects were likely predictable from preclinical animal models. METHODS: Three different preclinical animal models were used in laboratory rats â€“ electrical brain-stimulation reward, in vivo brain microdialysis, and conditioned place preference/aversion. RESULTS: SR141716 â€“ at moderate-to-high doses â€“ produced a right-shift in electrical brain-reward rate-frequency functions, produced inhibition of extracellular dopamine in the nucleus accumbens of the limbic forebrain, and produced conditioned place aversion. These effects are likely predictive of dysphoric effects in humans. We conclude that medication development in psychiatry and related fields ignores relevant preclinical data at its peril. FUNDING ACKNOWLEDGEMENT: Supported by the extramural research grant program of the U.S. National Institutes of Health (Grant R01DA03622), the Intramural Research Program of the U.S. National Institute on Drug Abuse (Research Projects Z01DA000478 and Z01DA000513), the Aaron Diamond Foundation, the New York State Office of Alcoholism and Substance Abuse Services, the Julia Sullivan Medical Research Fund, and the Old Stones Foundation.

Interaction of amphetamine and female reproductive cycle during interval timing in mice.

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Amphetamine-related hospitalizations and overdoses are increasing, and few treatment options are available. One understudied aspect of substance use disorder (SUD) is that females transition quicker from initial use to dependance, report more adverse withdrawal symptoms, and have higher cue-induced relapse rates. Therefore, it is critical to elucidate the neural circuits underlying sex differences in SUD. Cognitive dysfunctions dependent on striatal dopamine, such as impaired working memory and attention, may underlie factors driving SUD. We study interval timing, which is suited to examine SUD-related cognitive dysfunction as it requires working memory and attention and is dependent on dopamine in the dorsomedial striatum. Here, we investigated how sex and the female reproductive cycle impacts interval timing during withdrawal from amphetamine. We measured interval timing using a task requiring rodents to â€œswitchâ€• from one response port to another based on their time perception. Subjects were trained on this task, and given amphetamine (2.5 mg/kg ip.) for 14 days. Subjects then experienced withdrawal for 14 days. We observed that acute exposure to amphetamine resulted in earlier and greater variability of switch times. Additionally, during withdrawal, females in the estrus stage of their reproductive cycle displayed no deficit in interval timing. Conversely, males and females in the diestrus stage displayed later switch times. This suggests that amphetamine exposure produces changes in time perception 1) following acute exposure and 2) during withdrawal in an estrus cycle dependent way. We hypothesize that these deficits in timing result from altered dopamine dynamics in the dorsomedial striatum. We will test this hypothesis by monitoring dopamine release and calcium dynamics before, during, and after chronic amphetamine. These findings will provide detailed mechanistic understanding of how amphetamine use, withdrawal, and female cycle impact cognition. These discoveries may lead to novel pharmacological interventions for SUD. 5R01MH116043-04

IMAGING OF CALCIUM TRANSIENTS IN RAT HIPPOCAMPUS REVEALS STABLE PLACE CELLS CLUSTERED BY FIELD LOCATION

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Calcium imaging using GCaMP indicators and miniature microscopes has been used to image cellular populations during long timescales and in different task phases, as well as to determine neuronal circuit topology and organization. Because the hippocampus (HPC) is essential for tasks of memory, spatial navigation, and learning, calcium imaging of large populations of HPC neurons can provide new insight on cell changes over time during these tasks. All reported HPC in vivo calcium imaging experiments have been done in mouse. However, rats have many behavioral and physiological experimental advantages over mice. In this poster, we present the first (to our knowledge) in vivo calcium imaging from CA1 hippocampus in freely moving male rats. Using the UCLA Miniscope, we demonstrate that, in rat, hundreds of cells can be visualized and held across weeks. We show that calcium events in these cells are highly correlated with periods of movement, with few calcium events occurring during periods without movement. We additionally show that an extremely large number of cells recorded during a navigational task are place cells (77.3+-5.0%, surpassing the number seen during mouse calcium imaging), and that these cells enable accurate decoding of animal position and can be held over days with consistent place fields in a consistent spatial map. We then use statistical techniques developed in geographic mapping studies to demonstrate that cells that code for similar spatial locations form small clusters. Finally, we show that this clustering is not the result of artifacts from calcium imaging, and discuss implications of our data for in vivo imaging and the place field literature.This study was supported by: NIA T32-AG020506, NIA R37-AG008796, NINDS R01 NS113804

Organizational Features and Functional Implications of the Locus Coeruleus-Norepinephrine Projection to Motor Regions of the Rodent Brain

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The brainstem nucleus locus coeruleus (LC) projects broadly throughout the forebrain, brainstem, cerebellum, and spinal cord and is a major source for release of the small molecule transmitter norepinephrine (NE) in these areas. While we know much about the organization of the LC-NE system with respect to sensory and cognitive circuitries and the impact of LC output on sensory guided behaviors and executive function, much less is known about the role of the LC-NE pathway in motor network operations and movement control. As a starting point for closing this gap in understanding, we are using the intersectional recombinase-based viral-genetic strategy TrAC (Tracing Axon Collaterals) to characterize LC-NE projections to motor regions of the mouse brain. This technique allows us to not only map the distribution of LC-NE axons to target areas of the brain, but also to examine the distribution of their cell bodies within the LC and their dendritic fields within the peri-coerulear space. Initial results indicate that the deep cerebellar nuclei (DCN) receive input from a large number of bilaterally distributed NE-containing neurons. In contrast to the scattered distribution of LC cells that send axons to thalamic targets, LC-DCN projecting cells are more heavily concentrated in the core of the nucleus. The dendritic fields of these cells are directed into the dorsal medial, ventral medial, and lateral sub-regions of the peri-coerulear space. Lobules in the anterior cerebellum and posterior cerebellum also receive input from bilaterally distributed LC cells, but these cells are less numerous and more scattered than those projecting to the DCN. These results contrast with the scattered and predominantly ipsilateral (95%) distribution of the NE-containing cells that project from LC to cerebral cortex including the primary motor cortex. Ongoing studies are targeting the red nucleus and lateral vestibular nucleus to further probe the organization of the LC-NE projection to supraspinal motor centers. The overarching goal of this work is to determine the distribution of motor network projection neurons within LC, visualize their dendritic fields in the peri-coerulear space, and examine the distribution of their axon collaterals. The expectation is that this information will establish a foundation for future studies aimed at elucidating the role of the LC-NE system in motor control. Supported by start-up funds from Rowan University School of Osteopathic Medicine to BDW.

Chronic ACE2 inhibition, similar to that caused by SARS-CoV-2 infection, causes cognitive impairment in mice that correlates with hippocampal oxidative stress and neuroinflammation.

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Chronic ACE2 inhibition, similar to that caused by SARS-CoV-2 infection, causes cognitive impairment in mice that correlates with hippocampal oxidative stress and neuroinflammation.Heather Macarthur1, Subhashis Banerjee2, Michael Niehoff2 and Susan Farr1,2Depts. of Pharmacology & Physiology1 and Internal Medicine2, Saint Louis University School of Medicine, St. Louis, Missouri, USA.“Long-haul COVID” is defined as health issues lasting more than four weeks after recovery from SARS-CoV-2 infection and it is emerging as a major health issue of recovery in patients. The long-lasting and debilitating effects of long COVID include cognitive impairment, reported as issues with memory, attention span and concentration. It is unknown presently if these issues with cognitive function will translate into long-term problems such as the acceleration of the onset of Alzheimer’s Disease (AD) and related dementias (ADRD) in affected individuals, but the implications for a future public health crisis in this area are serious. SARS CoV-2 infects cells via the membrane bound Angiotensin Converting Enzyme (ACE) 2, the enzyme of the Renin Angiotensin System (RAS) that produces the anti-inflammatory vasodilator Ang 1-7. The viral spike protein binds to ACE2, initiating a conformational change in the protein that allows the virus to enter the cell with ACE2 in tow and thus the normal function of ACE2 to convert the pro-inflammatory vasoconstrictor Angiotensin (Ang) II, to Ang 1-7 is lost in the process. The resulting imbalance in RAS favors the production of excess Ang II, and due to its pro-inflammatory nature, Ang II has been implicated in the development of cognitive issues associated with AD. We hypothesized that this imbalance in RAS during SARS-CoV-2 infection plays a major role in the symptoms of cognitive impairment in “long-haul COVID”. Using a mouse model we chronically inhibited ACE2 with the specific inhibitor MLN4760, over a similar time-course to the infection/recovery profile of SARS-CoV-2. Using the T-Maze foot shock avoidance model, and the Novel Object Recognition (NOR) model we showed that significant cognitive impairment does indeed develop in these mice, and this correlates with a robust upregulation of markers of oxidative stress and neuroinflammation in hippocampal tissue. This study was supported by grant funding from The Henry and Amelia Nasrallah Center for Neuroscience at Saint Louis University

The effects of pre-reproductive stress in female rats on maternal care and DNA methylation across generations

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Maternal care during the postpartum period influences offspring behavior and affects essential epigenetic processes, including DNA methylation in the offspring brain. The effects of maternal care can be transmitted across generations. We and others have shown that the effects of stress, during or prior to gestation, can also be transmitted across generations. Specifically, we showed that pre-reproductive stress (PRS) in female adolescent rats affects behavior, gene expression patterns and microRNA expression in first- (F1) and second- (F2) generation offspring. We also found microRNA changes in oocytes of PRS-exposed rats and showed that pre-reproductive treatment with fluoxetine (FLX) or the corticotropin releasing hormone receptor 1 (CRHR1) antagonist NBI 27914 (NBI) reverses several stress-induced phenotypes in offspring. Here, we asked whether PRS and drug treatment would affect maternal care and global DNA methylation in the medial prefrontal cortex and amygdala of exposed dams as well as their adult F1 and F2 offspring. We found that PRS led to decreased Self Care behaviors and increased Pup Care behaviors, particularly licking/grooming and nursing, while drug treatment had little effect. PRS also increased methylation in the amygdala of dams and their F1 male offspring, but decreased methylation in F2 females. Drug treatment altered DNA methylation in exposed dams as well as their F1 offspring. Maternal care variables differentially predicted methylation levels in offspring. These findings indicate that stress in adolescence, before pregnancy, alter post-partum behavior and affect methylation levels across 3 generations. Combined with our previous findings, these data raise the possibility that germline epigenetic changes and social mechanisms act in concert to impact adult offspring phenotypes.Funding:This work was made possible by grant support from Israel Science Foundation (ISF) 1481/20.

Dynamical management of potential threat with dopamine and direct and indirect pathway neurons in the tail striatum

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In natural environments, it is critical to properly assess both reward and potential threats for appropriate behavioral choices. Here we used a semi-naturalistic foraging paradigm to model avoidance of potential threats. In this paradigm, a thirsty mouse freely goes out of a homing area and enters a foraging arena to obtain a water reward. In test sessions, a predator-like object (monster) surges when a mouse approaches a reward. In the presence of the monster, mice failed to retrieve reward and fled into the homing area. Across trials, mice returned home earlier and earlier before the monster charged, indicating that mice learned to predict a potential threat. Over multiple monster sessions, mice gradually succeeded in acquiring reward. This task, thus, allows us to study various aspects of threat managements under threat-reward conflicts, such as threat avoidance, threat prediction and eventual overcoming. We found that ablation of dopamine neurons that project to the tail of the striatum (TS) impaired threat avoidance and prediction. Mice with ablation of dopamine receptor type-1-expressing medium spiny neurons (D1-MSNs) decreased avoidance of the monster, while mice with ablation of D2-MSNs exhibited intact avoidance but failed to improve success rate. D1-MSNs were more activated in avoidance trials (failure of reward acquisition) while D2-MSNs were more activated in successful trials, especially in later sessions. These results indicate differential roles of D1- and D2-MSNs in threat management: avoidance and overcoming, respectively. Overall, the current study provides; 1) a behavioral paradigm which can assess dynamic threat management system in naturalistic environment in mice, and 2) a basic principle of how D1- and D2-MSNs dynamically regulate different aspects of behavior under the control of dopamine.

New Tools for Optical Control of Oxytocin Signaling and Social Behavior

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Oxytocin is a neurohormone involved in critical biological processes from childbirth and milk ejection to social behavior such as pair-bonding and maternal behavior. Deficiencies in oxytocin signaling have been linked with several neuropsychiatric disorders. At the molecular level, oxytocin activates the oxytocin receptor (OXTR), expressed throughout the brain and body. Oxytocin modulates neuronal excitability and synaptic transmission in the brain. However, methods are lacking to precisely deliver and activate neuropeptides like oxytocin within specific anatomical regions of the brain and periphery with spatiotemporal specificity. To achieve spatiotemporal activation of oxytocin in mammalian tissue, we developed caged analogs of oxytocin designed to be functionally inert before photolysis, and irradiation with UV light causes the release of native oxytocin. We validated each caged-analog in cell culture using calcium assays and imaging. We further demonstrated the utility of the caged-oxytocin in brain tissue by performing whole-cell electrophysiological recordings in acute brain slices in mouse hippocampal CA2 and auditory cortex, which express OXTR. Photolysis of the caged-oxytocin with UV light activates OXTR+ neurons but is inert sans photolysis. We then combine this compound with an optofluidic cannula to deliver the caged-oxytocin with simultaneous photolysis in behaving mice. We uncage oxytocin in the left auditory cortex, which mediates the pathway in which virgin female mice retrieve vocalizing pups in distress. Lastly, we demonstrate the utility of caged-oxytocin in non-neuronal tissue like mammary tissue. This is particularly advantageous for optical spatiotemporal activation of non-neuronal cells where optogenetics is not compatible. Together, these results demonstrate that caging peptides are a robust tool for optical control of neuropeptides binding their endogenous receptor throughout the mammalian brain and body. Funding: NIH, BWF

Evaluating theoretical models of hippocampal mapping in complex environments across protracted experience in freely-behaving mice.

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Abstract: Survival requires that agents learn useful representations to navigate space effectively, including responses to dynamic changes in environments across experience. The hippocampus is known to have an important role in representing the environment, and disruption to hippocampal circuits severely impairs navigational abilities. Such results have stimulated the development of numerous models on cognitive mapping in the hippocampus and its role in cognition and behaviour. Importantly, such models often make different, but overlapping claims about cognitive maps - from their generation, response to environmental change, and their relationship to behaviour and experience. Until now, there has been no consensus on how to compare such model-based predictions to empirical observation, and adjudicate between competing views. In the present study, we conducted a series of systematic environmental manipulations while tracking activity in large neural populations in hippocampal area CA1 across protracted experience in freely-behaving mice with single-photon calcium imaging. We show that repeated geometric and topological deformations of environments produce reliable shifts in representational structure observed in neural activity of CA1, and that greater organization develops with experience. Next, we generate predictions from theoretical models on hippocampal mapping using only animal behaviour as input, and compare our empirical observations to model-based predictions using representational similarity analysis (RSA). With this approach, we demonstrate that specific models show measurable improvements in predicting representational structure in CA1 population activity and its response to systematic changes in environmental geometry and topology. Our findings thus support the use of such datasets to benchmark theoretical developments and demonstrate the utility of RSA-based approaches to perform model-based comparison. This work was supported by CIHR Project Grant awarded to MPB, CIHR and FRQS Postdoctoral Fellowships awarded to JQL, and a NSERC Postdoctoral Banting Fellowship awarded to ATK.

Sex differences in the effects of chronic nicotine on the murine hippocampus during contextual fear extinction

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While 90% of Americans will experience a traumatic event, only 8% will present with Post Traumatic Stress Disorder (PTSD) during their lifetime. Biological sex is a major risk factor for the development of PTSD, with women being twice as likely to suffer from PTSD than men. Additionally, there is a bidirectional relationship between smoking status and PTSD. People suffering from PTSD are twice as likely to smoke daily than healthy controls, and people who smoke daily are twice as likely to suffer from PTSD. The relationship between smoking and PTSD is sex specific. Nicotine dependence is positively correlated with PTSD symptoms in men, while no correlation was observed in women, suggesting a sex specific neurobiological response to trauma resulting in an increased risk of smoking. The hippocampus has a well characterized role in both memory and emotion making it a prime target for investigating the mechanist link between PTSD and nicotine dependence. Specifically, the dorsal hippocampus (DHIPP) is responsible for learning and contextual memory, while the ventral hippocampus (VHIPP) is integral in affective responding. To elucidate the hippocampusâ€™ regiospecific role in the link between smoking and PTSD, we chronically treated male and female 7 to 8-week-old mice with either saline or intermittent nicotine (18 mg/kg/day) via osmotic minipumps (Alzet 1002 model). On the twelfth day of treatment, the subjects were trained in a fear conditioning paradigm with two CS-US pairings (CS 89 dB tone and US 0.35 mA shock), then underwent 6 contextual fear extinction sessions. Following behavioral testing, the DHIPP and VHIPP were collected and assessed for transcriptomic and proteomic changes via qPCR and western blots. Preliminary results from these experiments suggest a baseline sex difference in contextual fear conditioning and extinction. Chronic nicotine did not impact the fear conditioning but had sex specific effects on contextual extinction likely related to differences in transcriptional control mechanisms. Further examination of the functional alterations underpinning treatment by sex effects in extinction behavior are ongoing.Support or Funding InformationNIH/NIDA grant DA044311

A working memory update: development of a novel procedure for assessing updating in rodents

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Working memory is the process by which a limited capacity of goal relevant information is maintained and flexibly updated in a form which is readily accessible and resists interference. These separate components of working memory (maintenance, updating, interference resistance) can be differentially impaired in different psychiatric disorders, making behavioral assays that test individual components of working memory critical for the development of novel therapeutics. While a diverse array of human behavioral paradigms are employed to assess these components, rodent assays typically only probe working memory maintenance, whereas investigation of mechanisms underlying updating and interference resistance have been limited. To address this gap, we developed a novel, operant working memory updating task for rats that builds off the backbone of the commonly used delay non match/match to sample (DNMTS/DMTS) tasks. On a given trial, one of two levers extend, and a stimulus light illuminates above one of the levers (sample phase) which the rat must then press, to retract the lever and extinguish the light. Following a delay of 1, 4 or 8 seconds, both levers extend, both stimulus lights illuminate and one of two auditory tones plays. The auditory tone signals whether the rat should choose the same (match) or opposite (non-match) lever than the one pressed during sample phase. This requires the animal to update information maintained in working memory and apply the appropriate rule to successfully complete a trial. After initial lever press training, 16 rats (male and female) progressed through 9 training phases (taking between 65-115 days to reach the final phase) and displayed higher than chance levels of accuracy at the 1, 4 and 8s delay during the last week of training (80%, 64% and 57%, respectively). The top 25% of rats performed at 90%, 74% and 67% accuracy across the same 3 delays. Accuracy on match and non-match trials was 66 and 67%, respectively, indicating no bias towards either response strategy. Ongoing studies using this procedure, will investigate the contribution of prefrontal cortical dopamine in facilitating working memory updating.

Dissociable regulation of effort-related decision making by mu and kappa opioid receptors

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The endogenous opioid system has emerged as a locus of dysfunction in those suffering from opiate use disorder and as a major target of translational research. Changes in cost/benefit decision making are characteristic of pathological opiate use, however, our understanding of how this system modulates decision-making processes at baseline is incomplete. Particularly, the contributions of different opioid receptor subtypes to decision making remains unknown despite the development and use of therapeutics that selectively agonize/antagonize these receptor subtypes. To address this, we trained 16 rats (male and female) on an effort discounting task which requires them to choose between a low effort/small reward and a high effort/large reward option with the effort cost of the high reward increasing systematically over a session in blocks of trials. Upon achieving stable performance, rats received the selective mu receptor antagonist Naloxone or the selective kappa receptor antagonist Aticaprant (0, 1, 3, 10mg/kg doses used for both drugs). Antagonism of mu opioid receptors significantly decreased choice of the high effort/large reward option. This effect was observed in both males and females, although the effect in females is greater in magnitude. These effects on choice were accompanied by increases in response latency and omissions. Furthermore, preliminary data suggests that kappa receptors may also modulates effort-related choice in a sex dependent manner. Collectively, these data lend insight into opioid modulation of cost/benefit decision making and build a foundation for understanding how the use of opiate drugs can alter decision making in humans.

Opposing amygdala-striatal pathways allow chronic stress to accelerate habit formation

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When making a decision, we assess our potential actions and their consequences which allows us to adapt when situations change but is cognitively taxing. Oppositely, we also use habits, a more resource-efficient but inflexible strategy, executed based on past success and without thought of their consequences. Balance between actions and habits permits adaptive and efficient behavior. However, overreliance on habit is an endophenotype of many psychiatric conditions. Stress is a major contributing factor to these conditions and can tip the balance of behavioral control towards habit. The neural mechanisms that allow this to happen are unclear. Thus, the goal of this project is to reveal the neural mechanisms by which stress hastens habit formation. Evidence suggests the dorsomedial striatum is indispensable for goal-directed learning. The basolateral (BLA) and central (CeA) regions of the amygdala are known stress hubs in the brain. Direct excitatory BLA-DMS projections have long been known to exist. However, recent evidence revealed the CeA projects to the dorsal striatum. We have identified inhibitory CeA projections primarily target the DMS. Thus, BLA and CeA send opposing signals to the DMS, which are well positioned to regulate the influence of stress on behavioral control. To examine whether BLA-DMS and CeA-DMS projections mediate the influence of stress on habit formation, we coupled pathway-specific chemogenetic manipulations with a task we developed to model stress-induced acceleration of instrumental habits in mice. We found CeA-DMS activity opposes goal-directed learning and permits stress to accelerate habits. Conversely, BLA-DMS activity opposes the influence of stress on habit formation, rescuing normal goal-directed behavioral control. These data establish a function for the newly-discovered CeA-DMS pathway and indicate that amygdala-striatal projections differentially regulate the influence of stress over flexible and inflexible decision making. This has important implications for conditions influenced by stress and characterized by maladaptive habits. This work was funded by NIH R01DA046679 (KW), NIH T32DA024635 (JG), NIH TL4GM118977 (NP).

MMA fighters and epigenetics: an analysis of DNA methylation and miRNA expression

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Psychological and physical stress can induce dysregulation of gene expression via changes in methylation and miRNA expression. Such epigenetic modifications are yet to be investigated in professional MMA fighters who are subject to highly stressful training involving repeated head trauma. The fighters tested in the current study train at the highest level of striking and grappling, often following hypocaloric diets in preparation for professional competition in front of a global viewing audience. This study examined differences in expression of miRNAs associated with inflammatory disease in elite MMA fighters compared to active controls. PCR array was used to estimate differential expression in pooled samples of 21 fighters and 15 controls for 192 different miRNAs. Real time qPCR was then employed to quantify the expression of miR-155 in individuals of both groups. Global methylation differences between groups were also assessed via a LINE-1 assay (surrogate global DNA analysis). DNA methylation changes associate with a variety of health markers (e.g. chronic inflammation, autoimmune disease, and various cancers). An Independent-Samples t-Test found no significant difference in LINE-1 methylation between groups; however, an Independent-Samples follow up test found a significant difference in the expression of miR-155, suggesting a possible epigenetic mechanism responsible for chronic inflammation associated with professional level MMA training. Funding: NSU President's Research and Development Grant #335468

Methylation of genes and regulation of inflammatory processes on mental health outcomes in young adults with alcoholic parents.

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The experience of trauma can have a significant and long-term effect on a variety of behavioral and mental health measures, and enhanced risk of drug and alcohol abuse. Mental health is also linked to neural function, stress hormones and inflammation responses. Many college students are adult children of an alcoholic parent (ACoA), which increases risk of traumatic experiences and heritable and environmental epigenetic modifications. We examined the relationships between psychological function, inflammation, epigenetic modifications, and cortical activity in ACoAs. Measures of psychological health were assessed in ACoA college students and activity within regions of interest (ROIs) and biological markers of chronic inflammation, were compared between resilient and vulnerable groups. Vulnerable ACoAs reported more anxiety and depression behaviors, posttraumatic stress symptoms, and increased plasma C-reactive protein (CRP) as compared to resistant ACoAs. Vulnerable ACoAs also exhibited greater activity response to emotional cues as compared to resilient ACoAs and differing methylation on promoter and CpG island regions thought to influence regulatory control on serum CRP, glucocorticoid receptor function and influence emotional processing. These findings suggest a complex association between epigenetics, inflammatory regulation and psychological function that may be used in the future for early identification and intervention for mental health in ACoAs. KP was a SPURA fellow, NIDA grant number: R25-DA033674. This research was supported by a CBBRe Grant and South Dakota GOED Grant. Key words: Alcohol; Anxiety; functional Magnetic Resonance Imaging; Gene Modification; Depression; Immune System

Behavioral and neural alterations of the reward system by exposure to junk food in rats

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Different types of stimuli have attractive and motivational values that induce approach and consummatory behavior. The ventral tegmental area (VTA) is part of the brain reward system and is known to regulate these rewarding responses. The VTA is for example known to play a role in motivation and reward-seeking behavior. Previous studies have shown that excessive consumption of highly palatable food, like junk food, causes alterations in the reward system. A limitation of these studies, though, is that they solely focus on the responses to junk food, and do not study the effects of junk food on the reward system beyond the food reward. In this study, we assessed the neural activity patterns of the VTA during a 3-phase behavioral reward test, to investigate whether and how excessive junk food consumption negatively affects the reward system. For fiber photometry recordings, females received a unilateral infusion of a GCaMP6s expressing virus and implant of a fiber-optic cannula in the VTA. The rats were then exposed to either cafeteria diet (CAF, junk food), high-fat high-sugar pellets (HFHS) or standard chow (CTR) for 6 weeks, before their behavioral response and neural activation was assessed. First, the rats were tested 5 times with CAF as primary reward, followed by 3 sessions in which they could obtain access to a sexual partner (secondary reward). The final session contained standard chow as reward (dissatisfaction). After a reversal diet consisting of standard chow for 2 weeks, they were tested again. We hypothesize that CAF-rats will show less expectation, approach and consummatory behavior towards both the primary and the secondary reward compared to CTR-rats. Similarly, the neural activation of the VTA will be reduced in the CAF group during the three phases of motivational behavior for all the rewarding stimuli compared to CTR. We predict that HFHS-rats will show a similar behavior and neural activity as CAF-rats. In addition, we expect that these effects will last longer than 2 weeks on reversal diet. This study will contribute to explain the underlying mechanisms of the vulnerability of the reward system by the excessive consumption of junk food.This work was supported by Helse Nord (EMS) -HNF1443-19- and MSCA-IF (JFL) -882946-

Do different patterns of junk food exposure cause short-term and long-term neural adaptations in the reward system?

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Feelings of pleasure are mediated by the brain reward system. The mesolimbic pathway, which includes the ventral tegmental area (VTA) and nucleus accumbens (NAc), is the best characterized reward circuitry, but other brain areas and pathways are also involved in the responses toward rewarding stimuli. The orbitofrontal cortex (OFC), for example, plays a prominent role in decision-making and reward valuation. Although it has been shown that excessive junk food consumption affects the reward system, the underlying neural mechanisms are still largely unknown. Our study investigates the effects of different regimes of junk food exposure on the neural activity patterns in the brain. By analyzing the expression levels of the activity marker c-Fos, we will get an indication of short-term reactions of the brain to different food stimuli. Expression levels of the transcription factor Î”FosB on the other hand can show how junk food exposure can lead to long-term biochemical changes, which might be related to altered behavior. In this study, female rats were exposed to standard chow or cafeteria diet (CAF, junk food) for 6 weeks in different exposure regimes: i) ad libitum, ii) restricted at 30%, iii) intermittent for 1 day a week. At week 7, the animals were fasted at 7 am, and in the afternoon fed with either standard chow or CAF. Ninety minutes after feeding, the animals were perfused, and brains were collected for immunohistochemistry for c-Fos and immunofluorescence for Î”FosB in sections of the VTA, NAc and OFC. We hypothesize that intermittent or chronic exposure to CAF will result in decreased c-Fos expression in the VTA, NAc and OFC compared to restricted CAF or standard chow. On the other hand, chronic and intermittent administration of junk food could result in an increase in number of Î”FosB-IR cells compared to restricted CAF and standard chow. This project will contribute to explain the potential working mechanism by which junk food causes short and long-term effects on the main brain structures of the reward system.This work was supported by Helse Nord, HNF1443-19

Structural and functional sex differences in the ventral pallidal vasopressin system are associated with the sex-specific regulation of social play behavior in juvenile rats

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Social play is displayed by juveniles of many mammalian species, including rats and humans, and engagement in social play helps develop social competence throughout life. Autistic children show decreased involvement in social play, thus emphasizing the need to understand the neural mechanisms underlying social play. Here, we focused on vasopressin (AVP) acting in the ventral pallidum (VP) because AVP has been shown to regulate social play behavior and the VP is involved in social behavior. First, we examined the structure of the VP-AVP system in juvenile rats and found multiple sex differences, with denser AVP-immunoreactive fibers and denser AVP 1a receptor (V1aR) binding in males compared to females, but a greater number of v1aR+ cells in females compared to males. We then examined AVP inputs to the VP originating from the bed nucleus of the stria terminalis (BNST) and posterodorsal medial amygdala (MePD) and found no sex differences in the proportion of VP-projecting avp+ cells in either the BNST or MePD. Likewise, we found in both sexes that exposure to social play enhanced activation, as measured with fos, of VP-projecting cells in both the BNST and MePD. Next, we determined the involvement of intra-VP AVP signaling in regulating social play. To do so, we investigated whether exposure to social play altered activation of VP v1aR+ cells and we determined whether infusion of a V1aR antagonist into the VP altered the expression of social play behavior. We found that exposure to social play enhanced activation of VP v1aR+ cells in males only. Furthermore, V1aR blockade in the VP increased social play duration in males but decreased social play duration in females. Together, these findings demonstrate several structural and functional sex differences in the VP-AVP system that were associated with the sex-specific regulation of social play behavior by the VP-AVP system.

A transient beta oscillation occurs with high temporal regularity prior to stopping an ongoing movement

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Beta oscillations (~15-25 Hz) in the field potential are associated with immobility and controlling impulsive movements. The role of beta in movement control has been previously studied using the stop signal task, in which a cue instructs the subject to stop ongoing movement preparation. The time at which movement preparation stops is inferred from a 'race' model and provides an across-trial estimate of the movement preparation stop time. Thus, the alignment between trial-by-trial stopping and beta is imprecise. This may have led to the mixed findings across EEG studies in humans and monkeys. Moreover, the relationship between beta and stopping in rodents is unexplored. We used a new paradigm for head-fixed rats on a treadmill. The rats were trained to not run to a NoGo stimulus. On some trials, rats initiated a pre-potent running response but disengaged it before crossing a response threshold (distance). The peak velocity of these treadmill movements provides an unambiguous time when rats self-initiate stopping. We recorded 32-electrode EEG bilaterally over the entire cortex (39,366 trials, 306 sessions, 14 rats). Trial-averaged spectrograms centered on peak velocity revealed two distinct oscillations prior to stopping (9-12 Hz, alpha, and 15-25 Hz, beta). Larger movements were associated with more alpha and beta power prior to peak velocity. Moreover, alpha and beta were apparent on more electrodes indicating greater spatial spread with larger movements. These pre-stopping oscillations were observed globally but were more prominent over frontal and motor cortex. Thresholding trial-wise beta band-limited power (Z-score>2 relative to 1.0 s until 0.5 s before peak velocity) revealed 46 out of 56 bilateral frontal electrodes with a single beta burst preceding initiation of stopping by 145.1±27.3 ms (SEM across rats). Our data show that, when field potentials can be aligned to overt acts of stopping, beta power is a highly reliable predictor of the time of volitional stopping.

High fat diet feeding disrupts nucleus accumbens core regulated motivational control over food-seeking behaviour.

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Food intake is governed by homeostatic and hedonic mechanisms and is disrupted in obesity. The nucleus accumbens core (NAcC) is a hedonic regulator, mediating the metabolic control of food intake. This function can be studied using the general Pavlovian Instrumental Transfer (gPIT) paradigm, during which a stimulus predicting a food outcome is found to energize performance of an instrumental action earning another food outcome. This energizing effect is distorted in obesity-prone rats, in rats tested sated and in rats with abnormal functioning of the NAcC or its cholinergic interneurons (CINs). However, whether obesity-related brain insulin resistance can modulate gPIT and if this modulation involves a loss of insulin function on NAcC CINs is unknown. Here we investigated the effect of high fat diet (HFD) feeding and excision of the insulin receptor on NAcC CINs (Knockout) on gPIT. We used a dietary induced obesity protocol and Cre-Lox transgenics to assess gPIT when mice were hungry or sated. We found that gPIT was not disrupted in HFD and Knockout mice when tested hungry. When tested sated though, gPIT was abolished in Knockout and control mice but was left intact in HFD mice. This persistent food-seeking was associated with changes in NAcC CINs functioning, but not with changes to NAcC CINs insulin signalling. These results indicate that a HFD can disrupt the ability for motivational states to control gPIT, but that overeating despite a lack of hunger may not be driven by insulin resistance or insulin dependent mechanisms. This research was supported by an Australian NHMRC Ideas Grant.

Exploring parameters influencing social motivation in rats using social operant conditioning.

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The COVID-19 pandemic has led to protracted states of social isolation due to viral containment strategies, and elevations in the prevalence of psychological disorders including depression, insomnia, and substance use. Given the bolstering role that social support plays in mental health, a deeper understanding of mechanisms underlying social interactionâ€”particularly social motivationâ€” could have substantial transdiagnostic impact. Common rodent behavioural assays used to assess social behaviour capture social approach/avoidance, social preference, and social memory. However, they are limited in their assessment of social motivation. In contrast, the social operant conditioning model can provide valuable insights into factors that influence motivation for social interaction. Little is known about experimental parameters that may influence the acquisition and expression of social operant responding. This study investigated the influence of common variables used in behavioural neuroscience on acquisition of social operant responding: biological sex, time of day, and housing conditions. Additionally, using a behavioural economic model of social demand, we investigated how the sex of stimulus partner influences motivation for social reward. During 8 acquisition sessions (1h), rats were trained to lever press (FR1) for 60-s access to a social reward. Rats were either male or female, single-housed or pair-housed, and sessions were conducted either in the mid-late light phase (ZT6-10) or early-mid dark phase (ZT13-17). Rats were then trained on a within-session behavioural economic procedure to evaluate the impact of sex of social partner on social motivation. Biological sex significantly modulated acquisition of operant responding for social reward; on average, female rats obtained markedly more social rewards than male rats. Additionally, housing conditions significantly influenced social operant responding: on average, isolated rats acquired significantly more social rewards than pair-housed rats. Behavioural economics data examining the influence of stimulus sex will be discussed.

The effects of oral cannabidiol administration in male rodents: sleep, anxiety & proliferation.

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Cannabidiol (CBD) continues to rise as research on CBD's therapeutic uses (e.g., anxiolytic, analgesic, anti-stress, etc.) has shown promising results. However, CBD's effects and mechanisms of action require further exploration. Our project aimed to evaluate the pharmacokinetics (PK), and neurochemical and behavioral outcomes of a hemp-derived CBD compound from Ellipse Analytics (Denver, CO) through an oral administration rodent model. The PK profile of CBD was assessed by administering CBD (0, 5, 10, 20, or 40 mg/kg) to adult male Sprague-Dawley rats (n=10/group) for 10 days while drawing blood (1hr, 2hr, 4hrs) post-administration on the 1st, 5th and 10th day to measure plasma CBD levels. Then, CBD (0, 20, or 40 mg/kg) was administered to male rats over 10 days (n=6-16/group), with behavioral assays occurring on the 1st, 5th, and 10th day to assess pain, stress, anxiety, and sleep behaviors. Rats were sacrificed and brains were collected for analysis on day 11. Immunofluorescence will also be used to analyze levels of Ki67 (cell proliferation marker) and Oligodendrocyte transcription factor 2 (Olig2; oligodendrocyte marker) in the PK cohort. Our PK analysis showed a dose-dependent increase in CBD bioavailability with levels peaking between the 1st and 2nd-hour post-administration, and significantly decreasing by the 4th hour across all groups. Our behavioral results showed that 20mg/kg CBD reduced rodent inactivity over 6 hours, while 40mg/kg reduced corticosterone levels following a restraint stress test. These results offer support for CBD's potential therapeutic effect on both sleep and stress regulation. Future brain analysis will provide insight on Ki67 and Olig2 expression. Funding: Ellipse Analytics, Barber Fellowship, and McNair

Contributions of ventrolateral orbitofrontal cortex to flexible stimulus-reward learning under delay conditions.

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The brain can associate different reward attributes to a stimulus (stimulus-reward associations), including the probability of reward or the delay to reward; however, the relationship between the two types of learning is unclear. Here, we probed if stimulus-delay associations are learned similarly to stimulus-probability associations and the ventrolateral orbitofrontal cortex (vlOFC) contribution to these two types of learning. We trained male and female Long-Evans rats to discriminate two equiluminant visual stimuli, SA and SB, displayed on a touchscreen in pseudorandom left/right positions under two conditions: stimulus-probability discrimination where SA results in reward (p=1.00) and SB does not (p=0.00), both with a 1s reward delay; or stimulus-delay discrimination where SA results in a shorter wait time (0s) than SB (8 s), both with 100% reward probability. Rats were prepared with bilateral inhibitory (hM4Di, Gi) DREADDs or eGFP null virus on a CaMKIIa promoter in vlOFC and administered either clozapine-N-oxide (CNO) or vehicle (VEH) solution (3mg/kg, i.p.) 30 min prior to testing. Rats learned stimulus-delay faster than stimulus-probability discriminations even when the latter was fully predictive, and vlOFC inhibition significantly increased the selection of the stimulus associated with a shorter wait time. We then performed analyses using entropy-based metrics on the first and last sessions to probe strategy. We compared surprise in responses based on the chosen stimulus or chosen side following rewarded and unrewarded trials. Stimulus-based entropy decreased on the last relative to the first session. On the other hand, side-based entropy remained high throughout learning. We are presently conducting 1-photon calcium imaging using miniscopes to obtain the activity of single cells in OFC as rats learn. We find that single neurons in OFC respond strongly to reward events, and ongoing work is aimed at real-time decoding to predict if an animal will make a correct or incorrect choice based on neural activity in OFC. This research was supported by NIDA (RO1 DA047870 and R01 DA047870-S1).

Examining the impact of pubertal stress and adult hormone exposure on the PVN transcriptome

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Women who undergo adverse childhood experiences are at risk for lasting biological consequences, including affective and stress dysregulation. However, the mechanisms underlying this relationship are unclear. We have shown that pubertal adversity is associated with a blunted glucocorticoid response within the hypothalamic-pituitary-adrenal axis in both peripartum humans and mice. In mice, we examined puberty-stress reprogramming in the paraventricular nucleus (PVN) of the hypothalamus, which initiates the HPA axis response. We found that pubertal stress led to an upregulation of six immediate early genes (IEGs) in the PVN of adult, pregnant mice. IEGs are stimulus-dependent transcription factors that have many important downstream targets. Separately, we showed that the pregnancy-associated hormone allopregnanolone is necessary and sufficient to produce the blunted stress response phenotype in pubertally stressed adult female and male mice. Here, we assessed allopregnanolone as the potential mechanism underlying pubertal stress-induced IEG upregulation. We hypothesized that administration of allopregnanolone would increase IEG expression in the PVN of pubertally stressed mice. Male and female mice underwent 14 days of chronic variable stress beginning on postnatal day 21. Pharmacological treatment and brain collection occurred in adulthood. Mice were given either allopregnanolone or vehicle via two separate subcutaneous injections (peripheral) or via intra-PVN cannulae (central) before brain collection. RNA from PVNs was isolated and gene expression was measured using quantitative real-time PCR. Peripheral allopregnanolone interacted with pubertal stress to alter gene expression in the PVN in a sex-specific manner but did not fully recapitulate the pregnancy-associated phenotype. If central allopregnanolone is linked to increased IEG expression in the PVN, we expect that selectively-administered allopregnanolone increased IEG expression only in pubertally stressed mice. These studies will provide novel insight into the mechanisms underlying female-relevant risk factors for stress dysregulation, a central endophenotype of affective disorders. Support: NIH grant HD091376

Brief exposure to environmental enrichment reduces cue-evoked sucrose seeking and consumption in mice.

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Exposure to cues (e.g. smell of food) associated with the food availability and consumption provoke reactions such as food cravings in humans and food seeking in animals. Although the mechanisms that promote such cue-evoked reactions are highly investigated in motivationally-relevant brain areas such as the medial prefrontal cortex (mPFC), little is known about the brain mechanisms that suppress cue reactivity. Interestingly, brief episodes of cognitive and physical stimulation through games and exercise have shown to reduce food cravings in humans. In laboratory animals, such stimulation is provided through the provision of environmental enrichment (EE) in the animalâ€™s housing using spacious cages and the addition of toys and tunnels, for instance. The aim of this study is to examine whether brief (1d) access to EE housing could modulate cue-evoked sucrose seeking and associated mPFC activity in mice. We found that following Pavlovian sucrose conditioning using 10% sucrose solution and an auditory cue, EE attenuated cue-evoked sucrose seeking. Additionally, EE attenuated home cage sucrose consumption. Therefore, brief EE attenuates the motivational impact of sucrose cues possibly by decreasing the rewarding value of sucrose. We are currently investigating the effects of brief EE on the cue-evoked activity mPFC neurons in real-time using fibre photometry to elucidate EE-induced alterations in the encoding properties of food cues. This work is funded by the UK Medical Research Council (MR/T03260X/1).

Melanin-concentrating hormone neurons differentially regulate feeding and arousal as a function of downstream projection area.

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Animals must make informed decisions about what to eat to maintain a proper balance of nutrients. Yet homeostatic need is not the sole factor in the decision to eat. Non-homeostatic motivators to eat, such as craving of sugary or fatty foods even when sated, are a contributor to human eating disorders. Melanin-concentrating hormone (MCH) neurons of the lateral hypothalamus and zona incerta are a relevant neural target for both homeostatic and non-homeostatic motivators to eat. MCH neurons project to many brain areas including the arcuate nucleus, nucleus accumbens, and cerebral cortex, and have a role in numerous behaviors including feeding, sleep, learning, and reward. We hypothesize that MCH projections to the nucleus accumbens (NAc) promote hedonic motivations to consume food but do not have a role in sleep-wake regulation. To address this hypothesis, we instrumented MCH-ChR2 mice with EEG/EMG headcaps and optic fibers either over the MCH neurons in the LH or their terminals in NAc and investigated how optogenetic stimulation affected feeding and sleep behavior in different behavioral contexts. When stimulation is delivered continuously, we observed that mice with stimulation of MCH neurons in the LH spent more time in REM sleep as well as transitioned into REM sleep bouts more frequently, while mice with terminal stimulation in the NAc did not show a sleep effect. When given the opportunity to choose between a port which delivers both food and acute optogenetic stimulation or a port which delivers stimulation alone, mice with terminal stimulation in the NAc show a preference for food paired with stimulation, while mice with cell body stimulation of all MCH neurons in the LH show a preference for stimulation alone. These results begin to elucidate a mechanism by which MCH neurons differentially regulate feeding and arousal as a function of downstream projection area.Funding: The University of Michigan NIDA Training Program in Neuroscience: T32 DA7281 (KLF), Magnificent Michigan Summer Research Fellowship (LK), NIH R01DK129366, Michigan Diabetes Research Center, Whitehall Foundation (CRB)

Sex differences in the effects of age on prefrontal cortex-mediated cognition in Fischer 344 x Brown Norway F1 hybrid rats

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Aging is associated with alterations in multiple aspects of prefrontal cortex (PFC)-mediated executive functions. Such cognitive alterations can be modeled in rats, but almost all such work to date has been conducted exclusively in males. With the recent availability of aged females, we began initial evaluations of young adult (6 mo.) and aged (22 mo.) Fischer 344 x Brown Norway F1 hybrid rats of both sexes in intertemporal choice, working memory, probabilistic reversal learning, and progressive ratio tasks, on all of which young adult and aged males have been shown previously to differ. In the intertemporal choice task, in which rats made choices between a small food reward delivered immediately vs. a large food reward delivered after a variable delay period, age differences in male rats and sex differences in young rats were not evident, which was inconsistent with previous findings. In the working memory task, where rats had to remember the location of a lever over a delay period, young adults of both sexes performed more accurately than their aged counterparts, although this age difference was less robust in females. In contrast, in the probabilistic reversal learning task, in which rats had to learn to discriminate between two levers that were reinforced at different probabilities and then switched multiple times per session, there was a large sex difference, with females performing more reversals than males. Finally, in the progressive ratio task, in which the number of lever presses required to earn a food reward increased with each successive reward earned, there were significant age effects, with young rats pressing more than aged. Data from this initial experiment suggest that aging may have qualitatively or quantitatively different effects on executive functions in males and females, and highlight the importance of using both sexes in studies employing animal models of cognitive aging. This work was supported by NIH grant RF1AG060778 (JLB, BS) and the McKnight Brain Research Foundation (JLB)

Ventral hippocampus activity during reward seeking is modulated by a history of low dose ethanol in mice.

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More than half of the 130 million people in the U.S. who consumed alcohol within the last month did so at levels and in patterns that are not consistent with disordered drinking. However, even subdiagnostic drinking levels can have neurobehavioral outcomes. Clinical studies have shown that low levels of acute ethanol drinking soon after learning enhance task consolidation and memory recall. Our data in C57BL6J mice show that a history of repeated, low dose ethanol (0.5g/kg) exposure increases sucrose reward motivation in a progressive ratio (PR) task. The ventral hippocampus (vHPC) is increasingly considered a critical contributor to reward seeking and is sensitive to chronic ethanol exposure at higher doses. The present study investigated whether daily, post-training, low dose ethanol exposure modulated vHPC activity during motivated behavior. To investigate this, mice were implanted with arrays targeting the vHPC and trained to self-administer sucrose. One hour after all training sessions, mice were injected with low dose ethanol or vehicle. Neural activity in the vHPC was recorded during a PR task and analyzed surrounding key behavioral events, including lever pressing (reward seeking) and magazine entries (checking for reward). Results demonstrate that vHPC activity was suppressed following a lever press in saline controls. In contrast, this suppression was shifted in ethanol-exposed mice, occurring prior to a lever press. vHPC activity surrounding magazine entry was not modulated by ethanol exposure; both saline and ethanol-exposed mice showed reduced vHPC activity prior to magazine entry. These results suggest that a history of post-training low dose ethanol exposure modulates vHPC activity during reward seeking. Further, this shift in vHPC suppression around a lever press may be associated with enhanced sucrose motivation in ethanol-exposed mice. Future studies will use closed-loop optogenetics to investigate this possibility. A greater understanding of the neurobiological substrates impacted by low dose ethanol exposure can help identify factors placing casual drinkers at risk for transition to alcohol use disorder.This study was supported by NIH R00AA024499 (JMB), R21AA027629 (JMB), and F31AA029621 (KGB).

Oxycodone self-administration during pregnancy disrupts offspring ultrasonic vocalizations: Role of the dam-pup dyad in symptoms of neonatal opioid withdrawal syndrome.

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The use and abuse of opioids has increased dramatically over the past decade, resulting in a fivefold increase in the number of infants experiencing neonatal opioid withdrawal syndrome (NOWS). To date, the factors influencing NOWS severity as well as the relationship between NOWS and long-term neurodevelopmental effects remain unknown. Based on our previous findings reporting alterations in ultrasonic vocalizations (USV) in oxycodone-exposed pups and disrupted maternal behavior in rat dams following oxycodone self-administration during pregnancy, the current study used a cross-fostering design to determine whether USV number and/or quality is primarily influenced by dose-dependent exposure to oxycodone in utero or by the maternal behavior of the dam. Female Sprague-Dawley rats were surgically implanted with a jugular catheter and trained to self-administer oxycodone in daily operant conditioning sessions (2h/day, 5 days/week for 2 weeks, 6h/day 5 days/week for 1 week; fixed ratio (FR1) schedule; 0.1 mg/kg/infusion). Once females were pregnant, they had daily access (7 days/week) to operant chambers and were allowed to self-administer oxycodone for 6h/day. On the day of parturition, all operant conditioning ceased (forced abstinence), to induce withdrawal during the early postpartum period. On postnatal day 1 (PND1) litters were culled to 4 females and 4 males, and cross-fostered with litters from time-mated drug naÃ¯ve donor mothers. Pup USV and maternal behaviors were analyzed on PND3, 6, 9, and 12 using DeepSqueak. Preliminary data suggest that oxycodone self-administering dams in withdrawal, raising pups from the control dams, have impaired maternal retrieval. Further, prenatal oxycodone exposure decreased the number of total USVs throughout development and increased their complexity at PND3. Additional analyses in progress will determine the extent to which the amount of oxycodone self-administered during pregnancy correlates with postnatal outcomes independent of maternal effects. These data will be used to dissociate direct effects of oxycodone on pup neurodevelopment from those associated with altered maternal care.
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Investigating the Relationship Between Antioxidant Capacity and Stereotypy in Mice.

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Stereotyped behaviors are well-documented in patients with neuropsychiatric disorders (e.g., autism; schizophrenia) and in captive animals. Little is understood about what causes these repetitive and seemingly goal-less behaviors, and consequently, we lack a targeted therapeutic intervention for stereotypy. There is strong evidence, however, indicating that these behaviors observed in both populations arise from a shared underlying pathophysiology: oxidative-stress induced dysregulation of the indirect cortico-striatal pathway due to redox imbalance. Despite growing evidence for a relationship between the ability of the brain to buffer against radical oxygen species and the development of stereotypy, to our knowledge, no studies have directly assessed the relationship between these two phenomena. Understanding this relationship may shed light on new intervention strategies. Here, we used C57Bl/6 mice to assess the relationship between redox buffering capacity and stereotypy. We hypothesized that the bioavailability of Glutathione (GSH) (as measured via total GSH and ratio of oxidized to reduced GSH), and total antioxidant capacity, will both negatively predict the severity of stereotypy. To test this, we unobtrusively recorded home-cage behavior from male mice and are quantifying the presence of stereotypy using an established mouse ethogram. To quantify redox capacity, we collected blood and freshly voided urine samples which are being analyzed for bioavailability of GSH and total antioxidant capacity using commercially available enzyme immunoassay kits. We are currently in the early stages of analysis. Results and conclusions will be presented at the meeting. We acknowledge Stanford Universityâ€™s Department of Comparative Medicine for its financial support of this research.

The contribution of preexisting neural circuity to behavioral outcomes following social defeat stress in male and female mice.

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Stress is an established risk factor for the development of many disorders such as depression and anxiety. Substantial research efforts have resulted in groundbreaking discoveries, advancing our understanding of how stress alters the brain and body to result in behavioral dysfunction and pathology. However, a gap in the effectiveness of treatments remains in clinical populations. One contributing factor is the heterogeneous behavioral and neurobiological outcomes across individuals to stress. Some are susceptible while others display natural resilience even in the presence of extreme stressors. The majority of rodent studies thus far have aimed to uncover mechanisms of stress on the brain and body after stress exposure in those who are susceptible and largely in males. We have recently shown the brain displays circuity differences prior to stress exposure between mice who are susceptible and resilient. Here, we developed a model of social defeat (SD) stress, a well-validated model of divergent stress responses within a homogenous (in-bred) population, that includes males and females. In SD, aggressor male CD1 urine is applied to both male and female mice and a pair is exposed to an aggressor for 10 minutes followed by co-housing with an aggressor. This process repeats for 10 days total and is followed by a social interaction (SI) test to determine susceptible (avoidant) and resilient (social preference) phenotypes. There is a reliable population spilt (n= 56) with 40% of females and 50% of males displaying resilient behavior. To dissect how this preexisting neurocircuitry interacts with stress to result in behavioral outcomes we tracked the circuits within one individual by utilizing the TRAP2 mouse model, where activated neurons can be tagged within a specific temporal window alongside of immediate early gene staining. These techniques enable the ability to look at two connectomes in the same individual to uncover the neurocircuit mechanisms of how selective susceptibility or resiliency to stress emerges and evidence on how pre-existing circuit differences shape individual variability in stress-responses. 5R01MH111918 DD and 5T32MH015174 KA.

Dopamine antagonism during acquisition of the two-way active avoidance task in rats.

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Active avoidance plays a key role in both normal and pathological functioning. Despite considerable progress in our understanding of the mechanisms of avoidance acquisition in the past decades, much remains to be discovered. Accumulating evidence points to a central role for the dopamine reward system in avoidance acquisition. In the current study, we aimed to replicate the finding that pre-training systemic administration of a dopamine antagonist impairs avoidance acquisition in rats, using a two-way active avoidance task. Thirty-six male Wistar rats were subjected to a single avoidance training session, consisting of 30 pairings of a conditioned stimulus (CS; 3 kHz tone, 75 dB, 20s) with an unconditioned stimulus (US; 0.6 mA foot shock, 10s). Rats had the possibility to avoid the foot shocks by shuttling to a neighboring safe compartment during CS presentation. Twenty minutes before the start of training, rats received an intraperitoneal injection of D1 antagonist SCH 23390 (0.05 mg/kg, N = 12), D2 antagonist sulpiride (20 mg/kg, N = 12) or vehicle (N = 12). We found that pretraining sulpiride administration had no effect on avoidance acquisition. In contrast, pretraining administration of SCH 23390 significantly impaired avoidance acquisition. We also observed impaired locomotor activity throughout the training session following SCH 23390 administration. In line with this observation, we found a locomotion deficit when rats were given SCH 23390 prior to an open field test. Therefore, we cannot exclude that reduced locomotion drove the impaired avoidance learning observed after SCH 23390 administration, given that rats needed to shuttle from one side of the box to the other to avoid the foot shocks. In an ongoing study (N = 24, results will be available by June), we are evaluating whether a lower dose of SCH 23390 (0.025 mg/kg) can impair avoidance acquisition without affecting locomotor activity, as tested using an accelerating rotarod. This project was funded by BOFZAP Starting Grant 17/035 awarded to Bram Vervliet by the Research Council of KU Leuven.

Does exercise rescue the toxic effects from early life stress? An examination of exercise induced decreases in the inflammatory factor COX-2 in the hippocampus of C57/Black 6J Mice.

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Maternal Deprivation (MD) is a form of early life stress (ELS) that stimulates the production of a toxic microenvironment in the brain by the increase of reactive microglia. This toxic microenvironment is a catalyst to the mass degeneration of neurons in the brain linked with many neurodegenerative diseases that has been well documented in both animals and humans. Research indicated that exercise is a natural way to mitigate the toxic effects of this chronic stress by decreasing the amount of activated microglia in the brain. This research investigated if exercise could rescue from the toxic effects of MD by way of decreasing the amount of reactive microglia in the hippocampus. To accomplish this male c57/Bl6J mice were pair housed into one of two groups: either standard weaning (SW) or maternal deprivation (MD) and then into either sedentary (SED) or exercise (EX) housing. Maternally deprived mice were removed at PND 14, one week earlier than the SW group at PND 21. After one month post SW removal brains were collected and analyzed for inflammatory factors by quantifying Iba-1 and COX-2 in the CA1-3 regions of the stress-vulnerable dorsal as well as the stress resilient ventral hippocampus. An ANOVA showed main effects for MD and SW treatment (p=0.002) as well as for EX and SED housing (p=0.001) for both microglia and COX-2 positive reactive microglia count. An ANOVA also showed a trend in the interaction between housing and treatment (p=0.077) for COX-2 positive microglia. These data suggest that MD produces long lasting effects on inflammation in the hippocampus, and that exercise acts to rescue these toxic effects. This research was funded by the Schapiro Undergraduate Research Fellowship as well as the Randolph-Macon College Chenery Research Grant.

Genetic background determines adolescent hippocampal learning and gene expression after acute alcohol exposure

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Ethanol disrupts learning and memory, and the severity of these effects may vary by genetic background, sex, and age. To understand how genetics and sex contribute to adolescent learning outcomes after ethanol, we surveyed fear conditioning after ethanol in a panel of inbred mice. Adolescent (PND 38 +/- 3) male and female mice from 9 inbred strains [C57BL/6J, C57BL/6NJ, DBA2/J, 129S1/SvImJ, A/J, BALB/cByJ, BTBR T+ tf/J, C3H/HeJ, and FVB/NJ (The Jackson Laboratory, Bar Harbor, ME; n=9/sex/strain/treatment)] were treated with ethanol (1.5 g/kg, i.p., 20% w/v in 0.9% saline) or saline 15 minutes prior to fear conditioning training. Contextual and cued learning were tested one day later. Contextual fear learning was most sensitive to disruption by pre-training ethanol, with heritable (31%) freezing outcomes dependent upon both strain (p<0.001) and sex (p=0.046; females more impaired than males). Cued fear learning was also impaired by ethanol, although to a lesser extent than contextual learning, with heritable (18%) freezing outcomes dependent upon strain (p<0.001) and not sex. BEC assessment suggested that strain differences in learning after ethanol were not related to ethanol metabolism. Next, we conducted RNA-sequencing of the dorsal hippocampus, a region uniquely involved in contextual learning, in C57BL/6J and DBA/2J strains to identify genetic mechanisms involved in ethanol-associated deficits. We found unique ethanol- and learning-associated transcripts and pathways across strains. Collectively, we demonstrated a genetic basis for learning outcomes after ethanol exposure during adolescence in inbred mice and we have begun identifying neural pathways related to adolescent ethanol-related cognitive deficits.bFunding: T32GM108563 (L.R.S.), 1U01DA041632 (T.J.G), the Jean Phillips Shibley Endowment (T.J.G.), and Penn State University (T.J.G.).

Striatal acetylcholine reports distict update signals during flexible multi-step decision making.

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The striatum plays a critical role in coordinating reward guided decision making. It also has one of the highest concentration of markers for cholinergic transmission. Striatal acetylcholine (ACh), which is mainly supplied by a small population of cholinergic interneurons with extensive local arborization, exerts a powerful influence over neurotransmission and plasticity. A handful of electrophysiological studies show rewards and reward-predictive cues elicit ACh responses in simple behavioral tasks, and temporally coarse manipulations of striatal ACh suggest a role In rapid behavioral flexibility. However, historical technical challenges in measuring and precisely manipulating acetylcholine release in vivo have hampered the ability to refine our understanding of how striatal ACh shapes more complex behavior, such as when animals need to update sequential decisions in a structured environment. The recent advent of genetically encoded tools enabling measurement and manipulation of ACh levels with high temporal precision has rekindled interest in this area. Here we used the recently developed GRABACh3.0 sensor to characterize rapid ACh fluctuations in the nucleus accumbens core (NAc) and dorsomedial striatum (DMS) during a sequential reward guided decision-making task in mice. Probabilistic reward delivery enabled us to determine how ACh levels were shaped by reward expectations, and the action-state transition structure allowed us to measure ACh fluctuations while navigating changing action plans. Both NAc and DMS ACh carried time-locked information about (i) reward and reward expectations (though only by reward omission in DMS), (ii) value updates (inverse ‘reward prediction errors’), (iii) action updates, and (iv) movement (at distinct timepoints in DMS and NAc). These signals co-occurred with sustained information reflecting the recent local reward rate. Together, these findings suggest that NAc and DMS striatal ACh differentially contribute to flexible decision making by signaling unexpected changes in the environment. Funding Acknowledgements: National Science Foundation Postdoctoral Research Fellowship in Biology 1811713, Balliol College Dan Norman Fund, Wellcome Trust.

Science for all ages: What Quidditch can teach us about prefrontal cortex, the striatum, and the cerebellum.

Ava Hughes, Ishmam Bhuiyan, Daphne S. Ling. University of British Columbia, Vancouver, Canada. Funding: DSL - Canadian Institutes of Health Research Doctoral award and Institute of Mental Health award.

Science education has to start from young and continue throughout the lifespan. In this poster, we will demonstrate how learning from early childhood can be made fun through the use of daily activities enjoyed by the child and how these activities can be further built upon by educators in classrooms. For this, we have chosen to illustrate J.K. Rowlingâ€™s award-winning Harry Potter and the game of Quidditch Quidditch is a (fictional) 7-player game played on flying broomsticks where the goal is to score goals, avoid being bludgeoned by rogue flying balls, and to find a flying walnut-sized ball called the Golden Snitch; Harryâ€™s job is to capture that elusive Snitch. Many brain regions are required for Harry to successfully capture the Snitch, and we will focus on the processes and functions of three brain regions involved in Quidditch in this poster: prefrontal cortex, the striatum, and the cerebellum. Through a series of cartoons, we will depict how these three brain regions work together to make decisions, plan and execute a strategy to win the game, fine-tune his coordination while flying, and continually update strategies, and change course in real-time as the game unfolds. Science can be found in almost every aspect of our lives and as a result, there are countless opportunities to learn and expand our knowledge. But these opportunities to learn should not be confined to a classroom. In order to inspire students and increase classroom engagement, educators can look to derive scientific meaning from areas that are of great interest to students. For example, instructors can create assignments that require students to pick an Olympic sport and analyse the skills by tying it to how the brain produces those behaviours. Parents of young children can similarly do this at home by choosing an activity the child enjoys. These activities can help to improve both the retention of knowledge and motivation to learn. When we use daily events and activities as avenues for learning, we transform science into something fun.

Integrating neuroanatomy and behavioural neuroscience to enhance medical students' appreciation of visual processing.

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Behavioural neuroscience and neuroanatomy are often taught in isolation, leaving important context out of the information students are presented while learning about each topic. In this poster, we discuss the benefits of using neuroanatomy to enhance a studentâ€™s appreciation for behavioural neuroscience during their medical education. To accomplish this, we draw upon the experiences of medical students and instructors at the University of British Columbia, where neuroanatomy is integrated into the curriculum and is taught in tandem with relevant clinical presentations and aspects of human behaviour. Using human visual processing as an example, we demonstrate how structure and function are inextricably linked, and, as such, medical education benefits when they are used to complement each other. In this poster, we focus on two visual streams, their anatomical features, and relevant clinical presentations to demonstrate how neuroanatomy can improve medical studentsâ€™ comprehension of human behaviour. The dorsal and ventral visual streams are cortical pathways that originate in the primary visual cortex and project into the parietal (dorsal stream) or temporal (ventral stream) lobes respectively. The dorsal stream is involved in spatial processing and navigation, and integrates somatosensory information with visual information, whereas the occipito-temporal ventral stream projects to the temporal cortex to facilitate object discrimination and recognition. We will also discuss how specific lesions and clinical presentations, such as Balintâ€™s syndrome and visual agnosia, can be used to connect neuroanatomical structures with their behavioural functions. In understanding the deficits related to structural abnormalities in the brain, students are better able to appreciate the physiological function of these structures, and their role in behaviour. The reverse is also true. Form and function go hand-in-hand and an educational curriculum that appreciates both is essential.

Safety learning during thermal threat is affected by social isolation stress and requires prefrontal and hippocampal processing.

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Threat and safety learning are crucial for survival and adaption. The prefrontal cortex (PFC) and hippocampus (HPC) are strongly implicated in these functions. However, most animal studies to date have evaluated the contributions of these brain regions using traditional learning paradigms involving danger in the form of electric shocks. The contributions of these brain regions during more naturalistic forms of danger, however, remain unclear. In addition, there is great interest to understand how these brain regions and learning processes are affected by naturalistic stressors such as prolonged social isolation. In this study, we explore these issues using a novel paradigm in which mice learn to discriminate discrete zones within an apparatus that are paired with either really cold temperatures (~0Â°C, â€œthreat zonesâ€•) or pleasantly warm temperatures (~30Â°C, â€œsafety zonesâ€•). We also implement a 2-week social-isolation stress paradigm, as well as optogenetic and chemogenetic strategies to explore the contribution of distinct subregions of the PFC (prelimbic vs infralimbic), divisions of the HPC (dorsal vs ventral), and circuits among them. Results show that mice can optimally differentiate threat and safety zones using thermal stimuli, and optimally recall these zones later on even when these zones are no longer present. Surprisingly, a history of social isolation stress does not affect the learning of the threat zones, but profoundly affect the learning of the safety zones. In addition, our neural manipulation experiments revealed that selective inhibition of neural activity in the prelimbic-PFC can fully prevent the stress deficits on safety learning, whereas selective inhibition in the infralimbic-PFC mimics the stress deficits on safety learning. We also observed that inhibition of either the dorsal-HPC, ventral-HPC, or HPCâ†’PFC projections also mimic stress deficits on safety learning. Collectively, these findings indicate that prefrontal and hippocampal networks play crucial roles for safety learning in the presence of thermal threats, and that these neural networks are highly susceptible to social isolation stress.

Resource scarcity alters the basolateral amygdala transcriptome in a sex specific manner

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Experiencing adversity early in life can be a risk factor for the development of many psychiatric disorders, including Substance Use Disorder (SUD). Yet, most individuals exposed to early life adversity (ELA) do not go on to develop disorders. Stress that is not overwhelming can have an â€œinoculatingâ€• effect promoting resilience later in life. To understand how ELA impacts the basolateral amygdala (BLA), our lab used a rodent model of ELA called the limited bedding and nesting model (LBN), mimicking a low resource environment by restricting access to nesting materials during the first week of life. Previously we discovered LBN produces a resilient-like phenotype against addiction-related behaviors. LBN reduces impulsive choice, a behavior mediated, in part, by the basolateral amygdala. We also found that this model reduces morphine self-administration in male rats only. This suggests that LBN produces an inoculating effect against addiction-related behavior in males. We therefore sought to delineate possible molecular underpinnings that promote stress-induced resilience. RNA sequencing was conducted to delineate the effect LBN had on the transcriptional profile of the BLA in adult rats. BLA tissue from adult, behaviorally naÃ¯ve, rats were sequenced on an Illumina HiSeq 4000. We used Rank-Rank Hypergeometric Overlap (RRHO) to evaluate the degree of overlap in gene signatures between sexes. Differentially expressed genes (DEGs) were identified using an adjusted P value of<0.1 and a 50% change in the expression as cutoffs to determine significance. Many genes were upregulated by LBN in males and downregulated in females. We narrowed our analysis to genes showing a significant difference between control and LBN and found 209 DEGs in females and 149 DEGs in males. These gene expression changes were predominantly sex specific as only 11 genes demonstrate overlap. Heatmaps organized by fold change of LBN DEGs displayed different patterns of upregulated and downregulated genes in males and females. These analyses highlight unique patterns of gene expression LBN induces within the BLA in a sex-specific manner. Future work will focus on validating top targets with RNAscope and manipulating targets in a cell-type specific manner to directly link changes in gene expression to addiction-related behavior. Collectively, this work furthers our understanding of the neurobiological underpinnings of stress inoculation which may lead to advanced therapeutic techniques.

Psilocybin acutely reduces impulsive decision-making without affecting motivation.

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Substance abuse and gambling disorders are strongly associated with increased preference for risky rewards and reductions in impulse control, resulting in harmful consequences. Although these disorders are highly prevalent, there are limited treatments available. Previous research has indicated potential clinical benefits of psilocybin, but its role in impulsive decision-making has not been established. The serotonergic systems affected by psilocybin have established roles in decision-making, suggesting it may have significant effects. Therefore, this study investigated whether psilocybin impacts decision-making in probability and delay discounting tasks in male and female rats. In the probability discounting task, subjects chose between a certain, small reward and a risky, large reward that occurred with declining probability across days of testing. In the delay discounting task, animals chose between a small, immediate reward or a large reward delivered after increasingly longer delays across days of testing. Animals were administered 1mg/kg psilocybin via gavage prior to behavioral testing. Preliminary results suggest psilocybin decreases preference for the large, risky reward in the probabilistic discounting task and increases preference for the larger delayed reward in the delay discounting task. To determine if these effects are related to changes in motivation, subjects were further tested on a progressive ratio task, in which the number of lever presses required to obtain reward increases with each subsequent reward. We found no effect of psilocybin on total responses or breakpoints. This pattern of results suggests that psilocybin may have utility as a novel therapeutic for impulse control disorders. Funding for this project was provided by PsyBio Therapeutics, Inc.

EFFECTS OF AN OXYTOCIN RECEPTOR ANTAGONIST ON ESTROGENS FACILITATION OF ON SOCIAL RECOGNITION IN THE MEDIAL AMYGDALA OF FEMALE MICE.

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Social recognition (SR) is a critical cognitive skill required for animalsâ€™ successful participation in its social group and is widely regarded as crucial for individual survival. Estrogens and three of their receptors, ERï• ¡, ERï• ¢, and GPER1 have been shown to impact SR performance. Estrogens interact with other neurochemicals such as oxytocin (OT). Previous research has shown infusions of a subeffective dose of an oxytocin receptor antagonist (OTRA) into the medial amygdala prior to an infusion of 17-ï• ¢ estradiol (E2) into the PVN prevents E2 rapid facilitating effects on SR. E2 and agonists for all 3 ERs rapidly facilitate SR even when infused directly into the MeA. Whether an E2/OT interaction occurs also within the MeA, is unknown. If such interactions exist, then the OTRA will block the enhancing effects of E2 in the MeA, at a dose that does not block the natural occurrence of SR. 10nM and 25nM doses of E2 were employed, as they both facilitate SR in MeA. Ovariectomies were conducted to reduce circulating estrogen levels to those of diestrus, and cannulae were surgically implanted into the MeA. The test mouse was initially administered 75nM OTRA, previously shown to be a subeffective dose, or a vehicle of artificial cerebrospinal fluid (aCSF) into the MeA. After two minutes the test mice then received either 25nM or10nM of E2 or aCSF into the MeA. Next, the test mouse underwent a â€œdifficultâ€• social recognition paradigm. Additionally, an object recognition paradigm was employed to determine whether facilitating effects of 25nM E2 in the MeA were social specific. It was predicted that the infusion of the OTRA would prevent the enhancing effects of E2 in the SR paradigm, but these results would be social specific. Preliminary results indicate 10nM and 25nM of E2 when paired with aCSF facilitates SR, but when paired with the OTRA does not, supporting our hypothesis that E2 rapid facilitation of SR in MeA requires OTRs. Combined, this research program elucidates the mechanisms of estrogens, specifically those of E2, rapid enhancing effects on female SR in the MeA, which is a key component of the social brain. NSERC funding acknowledgement.

The effects of novel high-CBD cannabis on neuroanatomy in the Long-Evans rat.

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Cannabis, a drug derived from the plant Cannabis sativa, has been used both medicinally and recreationally for thousands of years. One particular phytocannabinoid in cannabis, cannabidiol (CBD), has many reported health benefits, including anti-inflammatory and analgesic properties, and is often sought after as a complementary modality. It is critical however, that these translational applications be supported by a foundational understanding of the effects of this drug on the brain and on behaviour. This project uses a rodent model to examine neuroanatomical outcomes following exposure to novel cannabis strains with high levels of CBD and low levels of THC (tetrahydrocannabinol; the primary psychoactive component of cannabis) and we hypothesize that these cannabis extracts will influence select morphological measures of rodent neuroanatomy. To address our hypothesis, Long-Evans rats were orally administered one of two unique high-CBD, low-THC cannabis extracts in peanut butter at either a low dose of 10 mg/kg, or a high dose of 40 mg/kg, for 10 days in adulthood. Control animals received no cannabis extract but followed an identical dosing/testing paradigm. Following cannabis exposure, changes in animal behaviour were assessed using a battery of well-established tests selected for their sensitivity to changes in the prefrontal cortex and hippocampus, two brain areas susceptible to the effects of cannabis. Animals were then euthanized, and their brains extracted for anatomical analysis. Measures of prefrontal and hippocampal synaptic connectivity, as well as gross measures of cortical thickness and thalamic area were taken from Golgi-Cox stained brain tissue. These cannabis extracts appear to have little effect on animal behaviour but generate specific changes in measures of synaptic connectivity. Thus, with limited anatomical and behavioural consequence, these high-CBD cannabis extracts present themselves as viable options for medicinal application. This work was funded by the Natural Sciences and Engineering Research Council of Canada, and Branch Out Neurological Foundation.

Alcohol-induced Changes in Decision Making and Neural Response to Negative Affect in Young Adults with Bipolar Disorder

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Alcohol use disorders (AUDs) occur in bipolar disorder up to five times more than that observed in typical youth. Data is emerging suggesting youth with bipolar disorder are more sensitive to alcohol with low levels of use associated with greater negative consequences. Mechanisms that contribute to increased risk for AUDs and related clinical consequences in bipolar disorder are unknown, but may relate to alcohol-induced changes in decision-making and paralimbic network activity. Data will be presented on how acute alcohol impacts decision-making and neural response to negative valenced stimuli in young adults with, compared to young adults without, bipolar disorder. To date, 35 young adults (49% with bipolar disorder; agemean=23 years, 62% women) have completed clinical evaluation, assessment of recent alcohol use, and placebo-controlled counter-balanced alcohol administration sessions. Participants were dosed to .08g% breath alcohol concentration. Following alcohol and placebo consumption, participants completed a Continuous Performance fMRI Task with Emotional and Neutral Distractors and the Iowa Gambling Task (IGT). Group by condition interactions on IGT performance were modeled and relations with recent alcohol use investigated. Alcohol-induced changes in neural activity were modeled and relations with IGT performance explored. In bipolar disorder, but not typical young adults, alcohol was associated with a decrease in reaction time following a monetary loss during the IGT (group by beverage condition p=.03). Across all participants, greater decreases in reaction time following a loss related to fewer past month drinks/drinking day (p=.006). Within bipolar disorder, alcohol, compared to placebo, was associated with decreases in insula activity during negative affect processing (p<.005) with decreases in insula activity inversely related to alcohol-induced changes in reaction time following a monetary loss on the IGT (p=.05). Preliminary results from this ongoing study, support differences in the acute effects of alcohol in bipolar disorder, compared to typical youth. Alcohol-related changes in sensitivity to negative affect may relate to risk for detrimental outcomes associated with alcohol use.This work was funded by K01AA027573.

Photobiomodulation of cytochrome c oxidase by chronic transcranial laser in young and aged rat brains.

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In cellular bioenergetics, cytochrome c oxidase (CCO) is the enzyme responsible for oxygen consumption in the mitochondrial electron transport chain, which drives oxidative phosphorylation for adenosine triphosphate (ATP) production. CCO is also the major intracellular acceptor of photons in the light wavelengths used for photobiomodulation (PBM). Brain function is critically dependent on oxygen consumption by CCO for ATP production. Therefore, our objectives were (1) to conduct the first detailed brain mapping study of the effects of PBM on regional CCO activity, and (2) to compare the chronic effects of PBM on young and aged brains. Specifically, we used quantitative CCO histochemistry to map the differences in CCO activity of brain regions in healthy young (4 months old) and aged (20 months old) rats from control groups with sham stimulation and from treated groups with 58 consecutive days of transcranial laser PBM (810 nm wavelength and 100 mW power). We found that aging predominantly decreased regional brain CCO activity and systems-level functional connectivity, while the chronic laser stimulation predominantly reversed these age-related effects. We concluded that chronic PBM modified the effects of aging by causing the CCO activity on brain regions in laser-treated aged rats to reach levels similar to those found in young rats. Given the crucial role of CCO in bioenergetics, PBM may be used to augment brain and behavioral functions of older individuals by improving oxidative energy metabolism.
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Do rats have partner preferences in social play?

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Rats, like many other species of mammal, engage in social play such as play fighting or rough-and-tumble play. The laboratory rat frequently play fights before reaching sexual maturity. This play has been shown to have effects on both neurological development and adult behavior; however, our understanding of play and the neurological effects come from studying rats housed and tested in pairs, in contrast to wild rats living in large colonies with many possible play mates. Partner preferences could affect the amount or quality of play experienced and cause variation in the consequences of playing. To test for partner preferences, we conducted two experimental tests with juvenile male Long Evans rats. Test one analyzed the patterns of play in groups of 6 rats that were cage mates. Eight groups were tested in 20-min trials from 30 to 38 days of age. Each trial was preceded by 2.5 h of social isolation and conducted in a large enclosure (80cm x 80cm x 50cm). This design determines if they have play preferences within familiar groups. Test two analyzed play in groups of 4 rats, from age 30 to 36 days old, using the same testing procedure as test one. However, in this paradigm, a focal animal was given a choice of 3 partners with which to play: one was its cage mate, the second was housed with the co-habiting pair but without physical access, and the third was a stranger. This design is used to determine if a previous social relationship affects their play partner preferences. For both experiments, the play behavior was scored to identify key behaviors of play (e.g., pounces, pins, chases) and their play partner preferences. This was determined using social network analysis. DeepLabCut, a program that provides multi-animal pose estimations, was used to determine if social preferences were driven simply by proximity to each other in the enclosure. The data to date show that rats do have preferred partners, which means that rats leave the proximity of one rat to play with one that is further away. However, the strength of such preferences is modified by an interaction of multiple factors such as familiarity, dominance, boldness, and play style. Not only does this group dynamics perspective increase our understanding of play, but it also provides insights into the consequences of play on the developing brain.Funding: Supported by NSERC [2018-03706].

Effects of acute lysergic acid diethylamide on intermittent ethanol and sucrose drinking and intracranial self-stimulation in C57BL/6 mice.

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Psychedelics, like lysergic acid diethylamide (LSD), are again being studied as potential therapies for many neuropsychiatric disorders, including addictions. At the same time, the acute effects of psychedelics on rewarding behaviours have been scarcely studied. The current study aimed to clarify if LSD decreases binge-like ethanol drinking in mice, and whether the observed acute effects on ethanol consumption are generalisable to a natural reinforcer, sucrose, and if the effects resulted from aversive or reward-attenuating effects caused by LSD. The effects of acute LSD were examined using 2-bottle choice intermittent ethanol (20%) and sucrose drinking (10%), discrete-trial current-intensity threshold method of intracranial self-stimulation, and short-term feeding behaviour assay in C57BL/6 male mice. The results showed that acute 0.1 mg/kg, but not 0.05 mg/kg, dose (i.p.) of LSD reduced 2-h intermittent ethanol drinking transiently without any prolonged effects. No effects were seen on intermittent 2-h sucrose drinking. The tested LSD doses had no effect on the intracranial self-stimulation current-intensity thresholds, nor did LSD affect the threshold-lowering, or rewarding, effects of simultaneous amphetamine treatment. Further, LSD did have small, acute diminishing effects on 2-h food and water intake. Based on these results, LSD decreases binge-like ethanol drinking in mice, but only acutely. This effect is not likely to stem from reward-attenuating effects but could be in part due to reduced consummatory behaviour. This work was supported by the Finnish Foundation for Alcohol Studies and the Finnish Cultural Foundation.

Characterization of novel clinically-relevant behavioral phenotypes in young adult Mucopolysaccharisosis IIIB mice.

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Mucopolysaccharidosis (MPS) IIIB is a lysosomal storage disorder caused by a complete loss of lysosomal enzyme alpha-N-acetylglucosaminidase, encoded by gene NAGLU, results in the inhibition of the breakdown of large sugars leading to the accumulation of heparin sulfate and serious neurological issues. Patients experience behavioral impairments beginning in early childhood with developmental delay, somatic issues like hearing loss, and progressing into cognitive deterioration, sleep disturbances, aggression, hyperactivity, social and emotional irregularities, and finally a lack of fear, motor decline, and dementia with early death. The MPS IIIB mouse model recapitulates clinical features including altered circadian rhythms, juvenile-onset hearing loss, later-age onset of balance issues and phenotypes suggestive of reduced fear. To understand the onset and progression of unexplored clinically-relevant areas in this model, we evaluated various domains of social, sensory, and conditioning behaviors with validated tasks. Behavior and health were monitored between 5-10 weeks of age. Both male and female MPS IIIB homozygous knockout mice weighed consistently more than their heterozygous controls littermates. Visual sensory thresholds performed using the Virtual Optometry System (VOS) in all mice at 6 weeks of age revealed deficits in acuity or contrast in KO mice. Social aspects such as preference, novelty and dominance were assessed using the three-chamber social approach assay and tube test. Territorial aggression toward a conspecific was evaluated in males with a resident intruder paradigm and processed using a deep learning pose estimation and behavioral predictive software. Sensorigating was assessed using auditory startle/pre-pulse inhibition and associative learning in the fear conditioning task. With life expectancy in the teens, early identification and intervention is vital. Our study using a mouse model of MPS IIIB provides much needed phenotypic information that will be useful in future evaluations of potential treatments. Funding Support: NICHD (P50HD103525, IDDRC@WUSTL).

Gtf2ird1 alone is not responsible for increased social motivation in a mouse modeling the Williams Syndrome deletion.

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The Williams Syndrome critical region, when deleted or duplicated, affects the expression of social behavior in humans, resulting in increased and decreased sociability respectively. The same region is syntenic in mice and the deletion, which causes Williams Syndrome, is modeled in the Complete Deletion (CD) mouse. Prior studies with the CD model show phenotypes similar to the features of Williams Syndrome, including increased sociability. However, only a single test was used to quantify social behavior and no specific genes within the region have been connected to the observed change. In this study, we present a more representative picture of the many facets of social behavior in the CD model by utilizing a diverse suite of social-related tasks, including the social approach setup originally used to identify the increased sociability, as well as other tests to assess motor and anxiety features. In addition, the contribution of a single gene in the region, Gtf2ird1, was assessed using a transgenic mouse line (TG-Gtf2ird1-HA), which overexpresses Gtf2ird1 with an HA tag to distinguish it from endogenous copies. By crossing the CD and TG-Gtf2ird-HA lines, four distinct progeny were produced allowing the comparison of 1) a wild-type within-litter control, 2) the complete WS region deletion, 3) Gtf2ird1 overexpression by itself, and 4) the complete deletion with rescued Gtf2ird1 expression. A social operant task revealed a significant increase in the breakpoint of mice with the complete deletion, suggesting the increase in sociability observed in CD animals may be driven by increased social motivation. Rescue of Gtf2ird1 expression on the CD background does not alter the social differences and Gtf2ird1 overexpression alone does not impact the breakpoint in either direction. This suggests Gtf2ird1 is not responsible for changes in the social motivation observed, despite previously being connected to social phenotypes. Mouse models were generously donated by V. Campuzano (CD) and J. Veenstra-Vanderweele (TG-Gtf2ird1-HA). Funded by NSF DGE-1745038, 5R01MH107515-05, P50 HD103525.

Social transfer of fear in group housed mice with autism-like phenotype

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Autism spectrum disorder (ASD) is characterized with, among others, impaired perception and understanding of others (a deficit in empathy and a construct within the Systems for Social Processes Domain of the Research Domain and Criteria framework). To study neuronal mechanisms underlying this deficit we need behavioral protocols which would reliably reproduce this phenotype in mouse models of the disorder. Such protocols would need to be ethologically accurate and devoid of human bias. The former can be assured with sufficient compartmentalization of the testing arena. The latter can be obtained through reduction of subjectsâ€™ interaction with the Experimenter and development of scripts for automated analysis allowing for longitudinal observations. Here we present data on social transfer of fear in group housed mice tested in the RFID-based Eco-HAB system. This protocol allows for characterization of responses of mice to the scent of cagemates exposed to a stressor outside of the experimental arena, as well as to their return to the cohort following such exposure. With its use we were able to show that BTBR T+ Itpr3tf/J mice, a mouse model of idiopathic autism, display aberrant responses to introduction of remote, social information about stress. These include delayed increase of interest in the fearful scent, increased incohort sociability in response to both the scent and the return of a stressed cagemate and more dramatic changes in social network dynamics to these events than those observed for the normosocial c57BL/6J mice. With further validation of these findings in other mouse models of ASD our results may lay ground for testing potential intervention strategies for treatment of empathy deficits in neurodevelopmental disorders.The study was funded by Polish National Science Centre grants 2015/18/E/NZ4/00600 to KM and 2017/27/B/NZ4/02025 to EK.

Pharmacological and neurophysiological effects of novel psilocybin-related tryptamines.

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Limitations in current antidepressants have resulted in a reevaluation of psychedelic tryptamines for their therapeutic potential. However, the widespread use of these drugs is complicated by federal regulations and unwanted side effects. Recently our lab has begun characterizing several tryptamines found in â€˜magicâ€™ mushrooms: baeocystin, norbaeocystin, and aeruginascin. Preliminary evidence suggests these compounds may rapidly alleviate depression without causing hallucinations, but the mechanisms and targets of these tryptamines are unknown. The overall purpose of this project is to determine the pharmacokinetics and neural effects of the psilocybin-related substances baeocystin, norbaeocystin, and aeruginascin. We found that all compounds have similar metabolic rate to psilocybin, and like psilocybin, each are dephosphorylated into active forms by alkaline phosphatase. In partnership with the NIMH Psychoactive Drug Screening Program, we found that both prodrug and dephosphorylated forms have significant affinities for a wide array of receptor systems, many of which are therapeutically relevant. Additionally, we found that blood brain barrier penetration varied widely among substances. Lastly, through in vivo electrophysiological studies, we found that tryptamines demonstrating therapeutic effects also altered the firing rates and local field potentials of medial prefrontal cortex neurons. Combined, these preliminary results suggest that many of these compounds may have significant therapeutic value, supporting further investigations in clinical studies. Funding for this project was provided by PsyBio Therapeutics, Inc.

Exposure to Perinatal Fluoxetine May Lead to Dysregulation of BDNF in the Hippocampus

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Depression is a debilitating disorder and as selective serotonin reuptake inhibitors (SSRIs) pass through placental and ductal epithelial barriers, there is an urgent need to understand the risks of exposure to offspring. Many studies suggest that early exposure to SSRIs may have long-lasting effects on offspring brain and behavior. Using animal models, perinatal SSRIs have been shown to correlate with increased aggression and increased anxiety-like behaviors in males. SSRIs have also been shown to influence several neurotransmitter systems including mature brain-derived neurotrophic factor (mBDNF) and its precursor, pro-BDNF. Though dysregulation of pro- and mBDNF has been associated with various mental health conditions, no study has examined both proteins in offspring after perinatal exposure. The aims of the current study were to examine the long-term effects of early SSRI exposure on anxiety, aggression, and BDNF proteins. For study 1, we hypothesized that exposed offspring would have higher levels of aggression and anxiety and in study 2, we predicted that mBDNF and pro-BDNF would be dysregulated. In both studies, we predicted differences to be more pronounced in males. Animals in the current study were exposed to fluoxetine (FLX; 5mg/kg/day) on post-natal day (PND) 2 until weaning (PND 21). On PND 120, adult offspring were tested for social anxiety using the social interaction test (SIT) and aggression on PND 122 using the resident-intruder (RI) test. Subsequently, both pro- and mBDNF were assessed using immunoassay. Results indicated that animals exposed to FLX exhibited lower levels of anxiety but no changes in aggression. Offspring also displayed increased mBDNF but not pro-BDNF, regardless of sex. Though we did not find a sex-dependent effects, the results of study 2 supported our hypothesis of BDNF dysregulation. These results are novel and suggest that offspring exposed to SSRIs via lactation experience lifelong consequences to behavior and neurochemical systems. This work was partially supported by Sigma Xi.

Levels of estradiol and progesterone are associated with fear acquisition and extinction learning differences in women.

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Risk for developing posttraumatic stress disorder (PTSD) is multi-determined; but in part depends on sex, with women having approximately twice the risk as men. Our lab uses translational tools in psychophysiology to understand the contributions of gonadal hormones (i.e., estradiol and progesterone) to PTSD risk in women. Fear learning processes underlie the pathogenesis and maintenance of PTSD, and fear extinction processes model exposure therapy â€“ a key treatment for PTSD. However, there is a dearth of preclinical research examining sex-related variables in laboratory fear conditioning models. Levels of estrogen and progesterone vary systematically throughout the menstrual cycle and are altered by hormonal contraceptive use; however, the impact of these hormones on fear learning processes has not been thoroughly examined. We measured changes in the acoustic startle response (defensive reflex) during a fear discrimination learning task in women and identified salivary levels of estradiol and progesterone sampled directly before fear conditioning. During fear acquisition, a neutral conditioned stimulus (CS+, danger cue) was paired with a threatening unconditioned stimulus (US) and a different neutral stimulus (CS-, safety cue) was never paired with a US. Ten minutes later, during fear extinction, both danger and safety cues were presented repeatedly without the US. We found that women with low estradiol discriminated between danger and safety cues sooner than those with high estradiol, and women with high progesterone acquired this discrimination sooner than those with low progesterone. For fear extinction, women with low estradiol failed to acquire extinction learning, still discriminating between cues at the end of extinction. Similarly, those with low progesterone failed to demonstrate extinction learning in the final block, indicating that low estradiol or progesterone could be related to deficits in extinction learning. These findings underscore the importance of considering ovarian hormones in fear learning and could provide insight into womanâ€™s increased risk of developing PTSD. Funding: NIMH 1R15MH125303-01.

Short-active gestational photoperiod reduces effortful choice behavior in mice, partial normalization by d-amphetamine.

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Seasonal birth patterns for several psychiatric conditions consistently reveal gestation under a winter-like light cycle as a risk factor. We recently demonstrated that winter-likeâ€"i.e., short-active (SA; 19:5 light:dark)â€"photoperiod exposure across gestation and early life (embryonic day 0 through postnatal day 28; E0â€“P28) induces psychiatrically relevant behavioral abnormalities in adult mice, including effortful amotivation in a progressive ratio breakpoint task and reduced immobility in the forced swim test (FST). Here, we sought to determine: 1) whether FST activity is driven primarily by prenatal (E0â€“P0) versus postnatal (P0â€“P28) photoperiod; 2) whether SA gestation reduces effortful choice behavior in a cross-species effort-based decision-making task (EBDMT); and 3) whether any such EBDMT deficits could be remediated by low-dose d-amphetamine (0.1 & 0.3 mg/kg, i.p.). Male and female mice exposed to prenatal (E0â€“P0), but not postnatal (E0â€“P28) SA photoperiod exhibited reduced FST immobility [F(2,21)=6.6, p<0.01]. Prenatally exposed (SA-born) vehicle-treated mice also demonstrated a baseline reduction in preference for high-effort/high-reward versus low-effort/low-reward contingencies in the EBDMT when there was an intermediate response costs differential between options [amphetamine dose Ã— response cost interaction: F(2,32)=6.3, p<.01; post hoc: t(22)=2.7, p<.05]. This effect indicates a deficit in effortful choice behavior and/or effort cost calculation similar to that observed in psychiatric populations. SA-born EBDMT performance was partially normalized by 0.1 mg/kg amphetamine [dose Ã— photoperiod interaction: F(1,14)=4.7, p<.05; post hoc: t(13)=-3.0, p<.05]. These data: 1) suggest a greater contribution of gestational versus postnatal light conditions to the behavioral alterations produced by perinatal SA photoperiod; and 2) implicate altered dopamine signaling in the behavioral phenotype of the SA-born mouse, and possibly in the etiology of winter-gestation-associated cases of psychiatric disease. Funding: UCSD Academic Senate Award (JY).

Fos-expressing neuronal ensembles in rat infralimbic cortex encode initial and maintained oxycodone seeking in rats.

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Neuronal ensembles within the infralimbic cortex (IL) as well as their projections to the nucleus accumbens (NAc) have been shown to mediate opiate seeking in well-trained rats. However, it is unclear if this circuitry is recruited during initial oxycodone self-administration. Here, we tested the necessity of IL neuronal ensembles in initial and maintained oxycodone seeking behavior using the Daun02 inactivation procedure. We trained male and female transgenic Fos-LacZ rats to self-administer oxycodone for 3hr daily sessions until rats met acquisition criteria (>30 active lever presses, >75% responding on active lever). We then infused Daun02 to selectively inactivate IL Fos expressing ensembles associated with initial oxycodone self-administration. We then tested the ratsâ€™ oxycodone seeking behavior 2 days later. We then repeated the experiment using a longer training period to determine the role of IL neuronal ensembles in oxycodone seeking after prolonged training. Here, we trained male and female transgenic Fos-LacZ rats to self-administer oxycodone in 3hr daily sessions under an increasing schedule of reinforcement for 9 days. After 1 week of oxycodone abstinence, we put animals through a 30 min induction test to reactivate neuronal ensembles associated with recall of oxycodone self-administration and infused Daun02 into the IL. We measured the ratsâ€™ oxycodone-seeking behavior 2 days later. We found that inactivation of IL neuronal ensembles reduced oxycodone-seeking after initial oxycodone self-administration on test day (t23=2.5, p=0.02). Next, we found that Daun02 attenuated oxycodone seeking behavior in well-trained rats (t17=2.6, p=0.02). In both experiments, Daun02 infusions decreased Fos-expression after the test, indicating ablation of Fos-expressing neuronal ensembles by Daun02. These results suggest that IL neuronal ensembles are formed during initial learning of oxycodone self-administration and are required for initial and maintained oxycodone seeking behavior. BLW was supported by a grant from the National Institute on Drug Abuse (NIDA: Grant No. 4R00DA042102-02) and a NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation. Oxycodone was supplied by the NIH Drug Supply Program.

Chronic unpredictable stress in female Wistar and Wistar-Kyoto rats subjected to progesterone withdrawal: relevance for Premenstrual Dysphoric Disorder.

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Premenstrual Dysphoric Disorder (PMDD) is related to an abrupt drop of progesterone in the late luteal phase of the menstrual cycle and impairments in the HPA axis that cause anxiety. Suffering females report higher daily-life stress and anxiety proneness that may contribute to develop PMDD, considered a chronic stress-related disorder. Currently, the effect of chronic stress in experimental models to explore PMDD has not been addressed. Thus, we explored the effect of chronic unpredictable stress (CUS) in rats subjected to progesterone withdrawal (PW) and we evaluated gene expression of components of HPA axis activation in the stress-vulnerable Wistar-Kyoto (WKY) rat strain, that is prone to anxiety behaviors. Female WKY and Wistar rats (control strain) were ovariectomized and randomly assigned to CUS or non-stressed group for 30 days. To induce PW, animals received 2 mg/kg of progesterone on day 25th for 5 days; 24 h later were tested in the anxiety-like burying behavior test. After behavioral completion, rats were euthanized and brain extracted to measure mRNA of CHR (PVN) and GR (hippocampus). Trunk blood was collected to determine corticosterone and vasopressin levels. Results showed that PW exacerbated anxiety-like behaviors through passive-coping in CUS-WKY. PW increased CRH-PVN mRNA and decreased GR-Hipp mRNA in both strains. CUS decreased CRH-PVN mRNA, in both Wistar and WKY relative to non-stress animals regardless of PW. Interestingly, GR-Hipp mRNA decreased only in CUS-WKY rats subjected to PW, and this may be related to higher corticosterone and vasopressin levels observed in CUS-WKY, suggesting impairments in the stopping mechanism of HPA axis in stress-vulnerable subjects exposed to CUS. Our findings aid to explain the neurobiology of anxiety in PMDD by showing that prolonged stress along with progesterone drop impair the HPA axis regulation and may facilitate anxiety in stress-vulnerable subjects

Sex steroids-Vasopressin interplay rapidly modulate social recognition and aggression in male mice.

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Social recognition (SR) is a pivotal skill that allows to identify previous investigated individuals and to emit appropriate pro-social or -aggressive behaviours. Sex steroids can rapidly affect SR and aggression by interacting with other neuropeptides involved in social behaviours such as arginine-vasopressin (AVP). The AVP system includes sexually differentiated brain regions, bed nucleus of the stria terminalis (BNST) and lateral septum (LS), which show more AVP neurons and fibers in males than in females. The steroids/AVP interplay impacts social and aggressive behaviours, although the mechanisms involved are currently poorly understood. To elucidate the rapid, non-genomic, effects of sex steroids on SR, adult castrated (CX) male mice were intracerebrally infused with one of 4 doses of T, one of 3 doses of 17ß-estradiol (E2) or one of 4 doses of dihydrotestosterone (DHT), targeting the BNST. Mice then underwent a difficult SR paradigm, in which CX mice showed an impairment. To assess aggression, mice were tested in a resident-intruder paradigm at either 35- or 120-min post-infusion to evaluate rapid and long-lasting effects. To investigate the interplay between sex steroids and AVP, CX male mice received the subsequent infusions of a specific antagonist for the AVP receptor 1a (α-VR1a) in the LS and of T, E2, or DHT in the BNST. Results revealed that infusing T, E2, or DHT in the BNST facilitated SR, with treated CX mice spending more time investigating a novel over a familiar CX mouse. In addition, all 3 steroids increased the dominance score in CX mice at 35-min, but only T and E2 showed a long-lasting effect, increasing the dominance score also 120-min after infusion. The infusion of α-VR1a in the LS prevented the facilitating effects of T or E2 in the BNST, but not those of DHT. These results confirm the existence of a BNST-LS circuit involved in SR and reveal a complex interaction between sex steroids and AVP mediating SR Elucidating the AVP-sex hormones interplay may lead to new therapeutic approaches for psychopathologies of social behavior with marked sex differences. This study was funded by NSERC.

Efficacy of Bremelanotide (Vyleesi) and melanocortin 4 receptors in the nucleus accumbens to enhance sexual motivation in female Syrian hamsters.

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Characterized by diminished interest in sex, disinclination to initiate sex, and a loss of pleasure during sex; disorders of sexual desire among women are not only poorly understood from a psychological perspective, but also in terms of their underlying neurobiology. This loss of sexual desire is a source of distress for many reproductive age women resulting in issues of low self-esteem and relationship conflict. This led to approval of the drug Bremelanotide, trade name Vyleesi, to treat hyposexual desire disorder in women. However, despite approve, very few clinical trials have been performed and almost nothing is known about its potential mechanism of action. Bremelanotide is a melanocrotin 4 receptor (MC4R) agonist; the melanocortin system is involved in the regulation of energy homeostasis and satiety. Thus, the following study investigated the role of Bremelanotide on sexual reward in female Syrian hamsters and the role of MC4R in the striatum. Female Syrian hamsters experienced five, two or zero 10-min sexual interactions (paired with an adult male) in the conditioned place preference (CPP) arena. Female hamsters that experienced two 10-min interactions were also subdivided into groups that received i.p. saline, 50 ug/kg or 200 ug/kg Bremelanotide 30-min prior to sexual experiences. Two or five days of sexual experience resulted in an increase in social preference ($p = 0.017$ and $p < 0.001$). However, neither a low (50ug) nor a high (200ug) dose of Bremelanotide enhanced sexual preference ($p > 0.050$). Bremelanotide also failed to enhance sexual behavior, as there were no changes in the display of the lordosis posture ($p > 0.050$). Following assessment of sexual motivation, brains were collected for assessment of MC4R expression in the striatum. mRNA expression of dopamine 1 receptor, dopamine 2 receptor and MC4R were carried out using Syrian hamster customized RNAscope probes. Collectively, these studies support the clinical ineffectiveness of Bremelanotide to enhance sexual motivation in women and support a role for MC4R expression in the nucleus accumbens for sexual reward in females. This work is supported by NIH grant R01 HD100007-01.

Early-life sleep deprivation and alcohol consumption: insights from a rat model.

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Adolescent alcohol use is a global health problem. More than 155 million adolescents reported heavy alcohol consumption (WHO, 2018). Several studies suggest that sleep deprivation may predispose adolescents to alcohol and substance use; however, the underlying mechanism(s) are not fully understood. The objective of this study was to investigate the effect of early life sleep deprivation (ELSD) on alcohol intake during adolescence. And to further investigate the microglia morphology in reward related brain regions following ELSD. Male Sprague Dawely rats were grouped into control (CON) or sleep deprived (SD). Rats were sleep deprived for 6-8 hours per day for 14 days from postnatal day (PND)19-PND32. At PND33, anxiety- and depression-like behavior were assessed in rats using elevated plus maze and sucrose splash test, respectively. At PND39, rats were assessed for alcohol consumption over a period of 5 consecutive days using two-bottle choice paradigm, water versus 5% ethanol. Microglia morphology and inflammatory markers were analyzed in reward related brain regions using immunofluorescent and western blotting. We found that SD rats exhibited significant anxiety- and depression-like behavior as compared to CON rats. Interestingly, SD rats consumed larger volume of alcohol when compared to CON rats which was significantly higher at day 5 (Mean of alcohol consumption (ml) Â± StD; CON= 6.67Â± 3.42; SD =19.00 Â± 6.05, $p = 0.0126$). SD rats also showed significantly higher preference for alcohol over water at day 5 (Mean of alcohol preference (%) Â± StD; CON= 26.85 Â± 14.97; SD = 57.69 Â± 5.61, $p = 0.014$. Alterations in behavior and increased alcohol consumption were associated with enhanced microglia activation within the reward-related brain regions. Data suggest that ELSD, most likely through microglia activation in reward related brain region, may affect reward seeking behavior indicated by increased alcohol consumption in adolescent rats.Funding: This research was funded by Small Grant Program and Bridge Funds awarded by the University of Houston to Dr. Samina Salim.

Pay attention to this change: Lateral Hypothalamic GABAergic neurons in attention and alcohol memories.

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During alcohol use, drug memories can persist throughout abstinence, and re-exposure to the cues that signal alcohol reward can lead to relapse. Recent studies suggest the GABAergic subpopulation of neurons in Lateral Hypothalamus (LH-GABA) are key players in memory processes, although the specific mechanisms through which LH-GABA encode and express memories are still understudied. In this study, we aim to describe how alcohol reward memories are encoded and expressed in LH GABAergic neurons. Using fiber photometry, we monitored LH-GABA calcium transients during acquisition and expression a cue-alcohol associations. In another group of rats, we inhibited these neurons during acquisition of the cue-alcohol association with optogenetics. We first trained the rats on an alcohol conditioning task in which they learned to associate one conditioned stimulus (CS+) with alcohol availability in a magazine (20% EtOH in water), while a different conditioned stimulus (CS-) was presented without consequence. We then tested expression of the memory by presenting the CS+ and CS- in extinction. Our results show LH-GABA initially respond to all incoming stimuli regardless of their valence, but this increased activity is maintained to reward-predictive stimuli (i.e. CS+), but activity decreased to the behaviorally irrelevant stimuli (i.e. CS-). In addition, we also found that LH-GABA activity decreased to below baseline during alcohol consumption. Moreover, in extinction this decrease is no longer present, but activity remains above baseline, potentially indicating that these neurons might be signaling reward prediction error in extinction. Finally, we also show that LH-GABA are functionally involved in the acquisition of cue-alcohol associations, as inhibiting these neurons during acquisition of such cues reduces alcohol seeking.

The ontogeny of alcohol-induced negative affect in C57BL/6J mice.

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There exists a high degree of co-morbidity between alcohol use disorder (AUD) and affective disorders, to which females may be more susceptible . The closing of the gender gap in under-age drinking and the pandemic-fueled spike in excessive drinking by mature adult women raises serious concern regarding the biopsychological impact of heavy alcohol consumption by females, during these developmental stages. Herein, male and female C57BL/6J mice underwent a binge alcohol-drinking procedure at various different developmental stages: adolescence (1 month-old), adulthood (2 months-old), mature adulthood (6 months-old) and aged/elderly (18 months-old). Mice were then assayed for negative affect in a 1-day behavioral test battery. Regardless of their age at drinking-onset, female mice binge-drank more alcohol than their age-matched males. However, alcohol intake declined progressively with age, although blood alcohol concentrations remained around the 80 mg/dL criterion for binge-drinking. Despite the sex difference in alcohol intake, we detected little evidence for sex differences in our measures of negative affect. Adolescent binge-drinkers exhibited little sign of withdrawal-induced anxiety, while adult binge-drinkers from all age groups exhibited a robust hyper-anxiety. We detected little evidence for any age-related change in baseline emotionality across adulthood. These observations highlight adolescence as a unique developmental period during which individuals are insensitive to the negative reinforcing properties of alcohol and provide novel evidence that, despite an age-related decline in alcohol intake, the severity of the withdrawal-induced negative affective state does not vary overtly with advancing age, likely due to an age-related slowing of alcohol metabolism. This work was funded by NIAA/NIH grant AA024044.

Cognitive relationships underlying risky decision making in male and female rats.

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The ability to evaluate risks associated with our choices is a hallmark of healthy cognitive function. Individual differences in risk-based decision making are associated with variability in other cognitive abilities, such as working memory. Many of these studies have been conducted in males, despite sex differences in risk taking. To address this, we behaviorally characterized male and female Long-Evans rats in a rodent model of risky decision making (Risky Decision-making Task; RDT) in which rats choose between a small, safe reward and a large, risky reward accompanied by an increasing probability of a mild footshock. After behavioral stability on the RDT, rats were tested in a battery of tasks to identify relationships between risk taking and measures of executive function in both males and females. Replicating previous work, females were more risk averse than males on the RDT. There were no sex differences in impulsive choice, risk taking involving uncertainty of reward delivery, working memory ability, or motivation to work for food. Females, however, displayed greater cognitive inflexibility than males in a set-shifting task. Although there were no significant correlations between choice behavior in the RDT and risk taking involving uncertainty, there was a significant sex-specific correlation between risk taking and impulsive choice in females, with greater risk aversion predicting greater impulsive choice. Similarly, greater risk aversion predicted better working memory only in females. In contrast, greater risk taking in males was associated with a greater number of errors during set shifting. There was no relationship between risk taking and motivation in either sex. Overall, our data suggest that distinct underlying cognitive processes mediate risk-based decision making in males and females. Specifically, the ability to make adaptive risk-based decisions in males may depend on the ability to flexibly shift behavioral responses as choice contingencies change. In females, risk taking may depend on the ability to retain information about past outcomes in working memory to guide future choice behavior. Supported by NIDA R00DA041493-3.

Serotonin receptor 7 stimulation rescues fear generalization in a PTSD transgenic mouse model carrying a truncated form of MeCP2.

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Post-traumatic stress disorder (PTSD) is an impairing mental disorder occurring after exposure to traumatic events. Invalidating symptoms are thought to arise from maladaptive memory processes and can include fear generalization to neutral stimuli. Current interventions display a high degree of resistance or relapse. The serotonin system has been proposed to play a role in dealing with stressful situations. Interestingly, male mice carrying an hypofunctional form of the methyl-CpG binding protein 2 (MeCP2-308 mice), an X-linked epigenetic modulator, are particularly vulnerable to negative outcomes of trauma exposure and have a reduced expression of the serotonin receptor 7 (5HT7R) in some key brain areas. The 5HT7R is involved in endocrine and behavioural responses undertaken to cope with stress, and in brain structural changes underneath memory processes, but its role in PTSD has not been investigated yet. Hence, we sought to evaluate the effects of 5HT7R pharmacological stimulation on PTSD-behavioural alterations displayed by MeCP2-308 mice. To this aim, MeCP2-308 male mice and wild-type (wt) controls were systemically treated for 7 days (0.25 mg/kg/day) with the 5HT7R agonist LP-211, starting 24 hours after the trauma (0.8mA unescapable footshocks). Mice were tested for cued and contextual fear memory recall (1st and 7th days of treatment) and avoidance of trauma-related stimuli (6th day). Trauma-exposed MeCP2-308 mice performed freezing when exposed to a novel context, suggesting that they generalized fear to neutral stimuli. Consistently, despite the absence of proper avoidance of trauma reminders, in the avoidance task traumatized MeCP2-308 mice exhibited increased fear regardless of the presence of trauma-related stimuli. LP-211 treatment normalized both freezing responses. Present data provide novel evidence for the potential involvement of 5HT7R in PTSD vulnerability, and suggest that 5HT7R agonism might prove beneficial for counteracting fear generalization. This study was supported by the Italian Ministry of Health (#GR-2018-12366210) to B.D.F.

Preclinical mouse study on maternal separation impacting childhood chemotherapy-induced cognitive impairment.

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Early (adverse) life events affect cognition and social behavior in later life. Exposure to chemotherapeutics can have long-lasting sequelae on behavioral and cognitive functioning in childhood-cancer survivors. Moreover, parental care might influence a child's resilience to adverse events. This includes the neurotoxic exposure to chemotherapeutics (chemo-brain), such as methotrexate (MTX), used in the treatment of the most prevalent childhood cancers. Therefore, the present preclinical mouse study investigates (1) the severity of MTX-induced socio-cognitive defects during weaning and adult life, and (2) how early life stress (maternal separation) affects the impact of MTX exposure. We implement a maternal separation or sham protocol in male and female C57BL/6 mice from postnatal day (P) 10 through 20. After weaning, pups are injected with MTX (100 mg/kg, i.p.) or vehicle on P21, P28 and P35, which mimics MTX exposure in children treated for acute lymphoblastic leukemia. We assess behavioral interaction in pups towards their dams (in comparison to unfamiliar adults) in a modified 3-chamber paradigm. Adult performance in MTX-exposed mice is assessed using an extensive test battery that includes a variety of exploratory, emotional, cognitive and social behaviors. We expect that maternal separation influences the animals' susceptibility to the socio-cognitive effects of MTX exposure. We shall discuss the broad relevance of these findings to our understanding of the late sequelae of chemotherapy, and the possible factors that could influence the increasingly prevalent condition of chemo-brain. This research is funded by the Fonds Wetenschappelijk Onderzoek (FWO) Vlaanderen and the Olivia Hendrickx Research Fund.

The rewarding nature of relief

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When a certain threat is about to happen, we tend to actively take actions to avoid a direct encounter with it. Whenever the expected threat is omitted, a pleasant feeling of relief emerges. However, the rewarding nature of this threat-omission-induced relief is still unclear. Since the relief might positively reinforce the active avoidance behaviors to prevent us from potential threats, impaired relief processing could result in less adaptive avoidance, leading to learned helplessness in the long run. Therefore, understanding the rewarding nature of the threat-omission-induced relief might contribute to the mechanisms of learned helplessness as we often see in depression disorders. The current study aims to systematically compare the processing of the monetary reward and the shock-omission-induced relief with different magnitudes in similar tasks within the same healthy individuals. The main hypothesis is that the reward and the relief are processed similarly at different levels (behavioral, subjective, psychophysiological, and neural), and the responses at all the levels increase linearly with the increases in magnitudes. We additionally include a decision-making task to assess the relative valuation of the relief versus the reward. In this task, visual stimuli representing different magnitudes of the reward and the relief are presented together at the same time and participants are asked to decide which stimulus to approach to obtain its associated outcome. We hypothesized that the processing of the reward and the relief with different magnitudes at different levels alone can predict the behavioral responses when choosing between the reward and the relief. Specifically, for each decision, we expect to see participants choose the reward when its responding is relatively higher compared to its competing relief, and vice versa. Finally, the trait of anhedonia is measured, which is known to impair the reward processing. If the relief is indeed rewarding, we expect to observe the similar effect of anhedonia on the threat-omission-induced relief.This work is supported by a Doctoral Fellowship of the Research Foundation â€“ Flanders, Belgium (FWO) [L, Leng, grant number 11J0921N].

Impaired fear memory in a BDNF Val66Met rat model is reversed by chronic exercise.

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The brain-derived neurotrophic factor (BDNF) Val66Met polymorphism is associated with reduced activity-dependent BDNF release in the brain and has been implicated in fear and anxiety disorders, including post-traumatic stress disorder (PTSD). Exercise has been shown to have benefits in affective disorders but the effects of long-term high levels of exercise or the role of BDNF Val66Met, remain unclear. Here we used a novel rat model with the rodent equivalent of Val66Met, Val68Met. We have previously shown that rats with the Met/Met genotype exhibit selective impairment of fear memory (IBNS 2021 and Translational Psychiatry, in press). Male and female BDNF Val/Val, Val/Met and Met/Met rats (n=9-13) were housed in automated running-wheel cages (Lafayette). Controls were housed either in standard cages or running-wheel cages with the wheel locked. The exercise animals developed compulsive wheel running with 600-1000 wheel revolutions/cage per night in males and 1200-1500 in females. There were no genotype differences in the amount of exercise. At 11 weeks of age, the rats were exposed to a standard three-day fear conditioning protocol, with three tone/shock pairings on day 1 (acquisition), and extinction learning (40 tones/session) on day 2 and day 3. Chronic exercise significantly increased freezing during the acquisition phase similarly in all genotypes and both sexes. As expected, extinction testing on day 2 revealed significantly lower freezing in response to initial cue exposure in control Met/Met rats compared to both Val/Val ($P = 0.003$) and Val/Met ($P = 0.03$) rats (impaired fear memory). Chronic exercise increased fear memory in Met/Met rats so that there was no longer a difference with Val/Val or Val/Met rats. There were no genotype effects on extinction memory on day 3 (not shown). Testing of the rats on the elevated plus-maze or in an open field revealed significantly increased anxiety in the exercise groups, irrespective of genotype. These results show that deficient BDNF release in the brain affects fear memory and that chronic exercise selectively reverses this genotype effect. However, chronic exercise at the levels observed here also led to an anxiety-like phenotype in all genotypes suggesting effects similar to chronic stress.

The effects of acute restraint stress in adolescent and adult rats on the brain and behavior.

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Stress exposure during adolescence exacerbates attentional impairments in many neuropsychiatric disorders, but the neurochemical bases of these impairments remain unresolved. Previous work from our lab has shown that healthy adolescent rats are more susceptible to distraction and more cognitively rigid than adult rats. These deficits have been linked to immaturity in the anterior cingulate cortex (ACC) and prelimbic cortex (PL), respectively. These same prefrontal sub-regions are critical to responding to acute stress. We hypothesize that acute stress in combination with high levels of attentional demands overloads these regions leading to severe attentional impairments. To address this, we exposed rats to one hour of restraint stress (stressed) or an equal amount of time in a clean cage with the restraint tube present (unstressed) prior to testing in a previously validated attentional set shifting task (ASST). The ASST measures distractibility, and the ability of subjects to form and shift an attentional set. Differences in cellular activity was measured in the ACC, PL, infralimbic cortex, orbitofrontal cortex, and locus coeruleus using c-Fos double-labeled for norepinephrine transporters. All stressed subjects, regardless of age showed an increased susceptibility to distraction compared to unstressed subjects. These results replicated prior work, showing that unstressed adolescents are more susceptible to distraction than unstressed adults and extended these findings to female subjects. Both stressed and unstressed adolescents had less cognitive flexibility than adults. Stress exacerbated this cognitive rigidity in adolescents. The current data suggests that all subjects show cognitive impairment following a single acute stressor. The negative effects of this single stressor persist longer in adolescents than adults. These findings contribute novel insights into how the immaturities in the adolescent brain confer specific vulnerability to acute stress. Future research will be aimed at determining how the timing of the acute stressor interacts with cognitive testing. Acknowledgements: Funding provided by the Cole Fund.

Social learning in mouse models of autism.

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Many rodent models of autism investigate simple social preferences but there is a paucity of information for any deficits in the learning, use and application of social information as occurs in human patients. There is also little direct comparison of how performance in social preference, dyadic social interaction and social learning relate to each other and if these assess the same social domains. Finally, it is also unclear if these social deficits are concomitant with adjunct behavioral abnormalities, such as motor, cognitive and emotional behaviors. Thus, we utilize a social fear learning task in a test battery that includes, social preference, dyadic social interaction, cognitive, motor and anxiety related behavior to examine the specificity and relationship of these tasks in murine mutants and negative controls. We used lupus MRL/lpr mice and mice with a Huntington mutation as non-autistic controls, C57 mice as unaffected controls, and mice with mutations considered to be related to autism spectrum disorders, including BTBR mice, FMR1 knock outs, Pten, Cntnap2 and ANKS1b mutants. We also compare these to male mice made aggressive via behavioral manipulations of mating and isolation housing. Support: IDDRC U54HD090260-01

Chemogenetic activation of VTA dopamine neurons affects operant responding for but not social play expression in adolescent rats.

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Social play behaviour is rewarding and important for the development of brain and behaviour. Disruptions of social play behaviour in rats have been associated with social and cognitive deficits. Social dysfunction is a hallmark of mental disorders that originate in childhood and adolescence, such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Catecholamine neurotransmitters, i.e. dopamine (DA) and noradrenaline (NA) have been implicated in social play, but the precise neural circuitry through which DA and NA modulate social play behavior remains elusive. With the use of designer receptors exclusively activated by designer drugs (DREADD) to specifically target the DA and NA innervation of the limbic forebrain in adolescent rats, we aim to identify the catecholaminergic mechanisms that modulate social play behavior in rats. Operant responding for social play was markedly enhanced by activating VTA-DA neurons in adolescent TH:cre+ rats compared to TH:cre- rats. The amount of social play behaviour in a 15 minute free play session was unaffected whereas locomotor activity was enhanced at higher doses of CNO in TH:cre+ rats. The present data adds to the pharmacological data on social play behaviour but also other rewards, i.e. elevating DA levels enhanced the motivation for but not the expression of social play behaviour in adolescent rats. Future experiments will determine the pathway specific contribution of enhancing VTA DA-neuron activity to the increased motivation to play. The work was supported by a NWO-ENW Veni grant (016.Veni.181.039).

Impaired amygdala plasticity and salience evaluation following environmental enrichment loss in rats.

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Psychological loss can erode well-being and precipitate depression. We attempt to emulate loss in rats by protracted environmental enrichment and subsequent removal to impoverished conditions. Previously, behavioral analyses revealed that enrichment removal (ER) generates loss-like phenotypes. Multi-omics and immunohistochemistry (IHC) indicated dysregulated immune signaling, cell-matrix communication, and parvalbumin input in the basolateral amygdala (BLA) of ER rats. Here, we further investigate these loss profiles and mechanisms utilizing BLA-centric behavioral tests. All studies feature 3 groups of adult male rats: environmentally enriched (EE), enrichment removed (ER), and control. EE and ER animals were housed in groups of 10 in large, multi-level cages with toys. After 4 weeks, ER animals were moved to single-housing, simulating the experience of loss. Two weeks after removal, one cohort of rats underwent fear conditioning, while another underwent passive avoidance, social avoidance, and acoustic startle. All rats were sacrificed 90 minutes after the final behavior to enable IHC examination of cFOS. In fear conditioning, ER rats acquired slower, extinguished faster, and showed weaker reinstatement. They crossed faster in passive avoidance and showed increased sociability in social avoidance, indicating impaired fear memory. They also exhibited enhanced acoustic startle reactivity. Altogether, ER rats exhibit a complex set of behaviors that revolve around salience evaluation, a key yet underappreciated role of the BLA which appears to be impaired in ER rats. This notion is further supported by IHC, which suggested decreased plasticity and increased inhibitory tone in the BLA following ER. This concept aligns with human profiles of loss, which often include emotional blunting. These behavioral and molecular mechanisms not only deepen our understanding of psychological loss, but also may reveal potential therapeutic targets for ameliorating loss.Funding: MH049698, F31MH125541

Prelimbic cortex encoding of reward-predictive cues following devaluation.

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Animals must modify their behavior based on updated expected outcomes in a changing environment. The prelimbic cortex (PrL) is necessary to shift behavior following outcome devaluation. To determine if PrL neuronal signaling is linked to the ability to shift behavior, we recorded PrL activity to reward predictive cues following outcome devaluation. Male Long-Evans rats (n=20) were presented with 2 cues as conditioned stimuli (CS+; predicting a sugar or food pellet) and 2 cues that did not predict a reinforcer. After 10 sessions, sugar pellets were devalued using a conditioned taste aversion procedure. Rats were tested under extinction to assess their ability to avoid the CS+ associated with the devalued outcome. The rats were then tested without either outcome delivered (re-exposure test). In both tests, rats spent less time in the food cup during the CS+ associated with the devalued outcome compared to the CS+ that predicted the ND outcome. PrL recordings revealed distinct cell populations that were excited or inhibited during the cues (classified as â€œphasicâ€•). We found that PrL neural encoding to the cue paired with the devalued reward negatively predicted the ability of rats to suppress behavior in the extinction test, but not in the re-exposure test. Also, the % of phasic neurons to the cue predicting the ND outcome was higher than to the cue that predicted the D outcome in the extinction test. PrL phasic responsiveness during the re-exposure test was no different to cues that predicted the nondevalued and devalued outcomes. While all rats were able to successfully avoid the outcome during conditioned taste aversion, a subset of rats continued to consume the devalued outcome in the re-exposure test. We found differential patterns of PrL neural encoding in the rats that did not avoid the devalued outcome during the re-exposure test compared to the rats that avoided the devalued outcome. These findings suggest that PrL neural activity tracks the updated outcome value post-devaluation. PrL neurons re-establish engagement during re-exposure test when both outcomes were delivered. Distinct phenotypes of rats may contribute PrL neural encoding to reward predictive following expected outcome value changes. R00DA042934 (NIDA)

Exposure to enriched environment reveals sex-specific behaviour modification in Cacna1c haploinsufficent rats

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“Breaking Expectations“, Philipps-University, Marburg, Germany 3Center for Mind, Brain and Behavior (CMBB), Philipps-University, Marburg, Germany 4KU Leuven, Psychology and Educational Sciences, Social and Affective Neuroscience Research Group, Belgium5KU Leuven, Leuven Brain Institute, BelgiumSeveral neuropsychiatric disorders have been associated with mutations in the Cacna1c gene encoding the pore-forming α1C subunit of the voltage-dependent L-type calcium channel Cav1.2. In the laboratory, an enriched environment (EE) consisting of objects which positively stimulate rats has been shown to mitigate behavioral phenotypes relevant to neuropsychiatric disorders. We leveraged ultrasonic vocalizations (USV) produced by rats in appetitive and aversive situations to study the effect of components of EE in Cacna1c haploinsufficient (Cacna1c+/-) rats. Specifically, we focused on the effects of repeated exposures to EE in male and female Cacna1c+/- rats and wildtype littermate controls. Here, EE comprised of a running wheel, a tunnel, a bridge, gnawing sticks, and a wire ball with hidden sweet treats on a layer of bedding under red light. We exposed 3 months old rats to EE for 1.5 hours every third day for 5 weeks (12 exposure events). We recorded their USV, exploration of the EE, interaction with enrichment objects and number of runs in the running wheel. Our results show that females displayed more runs in the running wheel than males. Also, running wheel usage was clearly lower in Cacna1c+/- rats compared to controls. More detailed analysis of the USV and visible behaviour of rats will help to clarify whether a perceived valence of EE and/or locomotor disparity underlies the sex- and genotype-specific behaviour suggested by our findings. Additionally, our experimental design enabled analysis of behaviour modification upon violation of an individual’s expectation of their environment since we prevented running wheel turns for the last 6 exposure events while other aspects of the EE were unaltered. Overall, our study will further our understanding of sex-specific behaviour changes induced by environmental factors in animals with genetic aberrations associated with neuropsychiatric disorders.

Paternal cocaine self-administration enhances fear-related behaviors and suppresses synaptic activity only in male progeny.

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Paternal exposure to cocaine induces epigenetic modifications that directly influence synaptic plasticity as well as memory- and reward-related behaviors. Given the high degree of comorbidity between substance use disorders and mental health illnesses, such as post-traumatic stress disorder (PTSD), we examined whether cocaine self-administration in male rats would produce fear-associated behavioral effects in drug-naÃ¯ve progeny. Adult offspring were subjected to cue-dependent fear conditioning, followed by cue extinction. We observed no differences in fear-related freezing behavior during conditioning. However, cocaine-sired male offspring exhibited deficits in extinction as well as increased freezing upon retrieval of the extinction memory, indicative of enhanced and persistent fear-associated memory relative to saline-sired controls. Consistent with our previous results with other behavioral models, we found no differences in fear-related behaviors in female offspring. To determine a physiological correlate for these behavioral results, we next performed patch clamp recordings in the amygdala, a brain region that is highly involved in the encoding of emotionally salient memories. Despite no differences in baseline physiological measures, we found deficits in long-term potentiation (LTP) at cortico-amygdala synapses in male, but not female, offspring of cocaine-exposed sires. Prior research heavily implicates this circuitâ€™s involvement in fear extinction, suggesting that the resilience to fear memory extinction observed in cocaine-sired male progeny may be due to inherited deficiencies in genes that govern LTP induction. Ongoing studies are therefore investigating whether paternal cocaine exposure affects the expression of several known candidate genes that play a role in synaptic plasticity. Funding Acknowledgement: Research was supported by NIDA grants R01DA033641, F32DA052993 and T32DA028874.

Post-training Glucocorticoid Receptor blockade in the mPFC promotes faster corticosterone recovery and contextual fear generalization in male rats.

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Acute stress may elicit a shift between memory systems during engram allocation, favoring the consolidation of reflexive responses instead of cognitive ones. Past studies suggested that increasing contextual fear conditioning (CFC) intensities elicit differential temporal dynamics of contextual specificity. Also, the mPFC seems to also be recruited in the systems consolidation of emotional memories; and corticosterone (CORT) treatment after moderate CFC facilitates time-dependent fear generalization, probably by influencing the shift of memory systems during consolidation. Here, we investigated in adult male Wistar rats whether the post-training infusion of the glucocorticoid receptor antagonist (mifepristone, MIF) into the PrL would modulate CORT response to a moderate CFC training and subsequent recent memory strength and specificity. Rats received 3 footshocks (0.6mA, 1s; considered as a moderate CFC) after a 2-minute exploration interval. Immediately after training, each rat received bilateral infusions of MIF (10ng) or vehicle (VEH) into the PrL. Thirty and sixty minutes after the end of the training, blood was collected from each animal for CORT quantification. Memory retention tests were performed 2 days after training. Freezing times in response to the training context during the test were considered as a measure of conditioned fear, and to the novel context as generalized fear. Both groups showed similar freezing times during training, and, even though CORT levels were similar between groups at 30 and 60 minutes, CORT's recovery rate was significantly faster in the MIF treated group. In the test, rats in the VEH group showed contextual discrimination whereas the ones treated with MIF generalized across contexts. CORT's recovery rate was positively correlated with generalization. Our results suggest that recent contextual fear specificity is dependent on GR activity in the prefrontal cortex, strengthening the hypothesis that fear generalization is a phenomenon associated with a shift in memory systems during memory encoding/consolidation. Funding: Sao Paulo Research Foundation, grants #2017/24012-9, #2017/03820-0.

Exercise and protection from stress caused by maternal deprivation in the hippocampi of female C57/Black 6J mice.

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Chronic childhood stress is known to cause changes within the hippocampus, resulting in negative cognitive effects and increased likelihood for developing neurodegenerative diseases. One model of early chronic stress is maternal deprivation, MD. While research into the negative effects of MD is well described, there are very few studies exploring how to reverse these effects. Exercise has been shown to improve the negative effects of stress such as increasing resiliency markers seen in BDNF and NPY and decreasing inflammation markers in microglia. For this research, female C57/BL6J mice were randomly assigned to a treatment (MD or standard weaning (SW)) and a housing (exercise (EX) or sedentary (SED)). The date of birth of the mice were designated PD0; MD mice were weaned at PD21, and SW mice were weaned at PD28. The mice were weaned either into sedentary housing, or into cages equipped with a running wheel for each mouse. Brains were analyzed in adulthood, 4 weeks after SW (5 weeks after MD). To determine if exercise increases resiliency in the brains of EX mice, levels of NPY and BDNF were quantified. To determine if exercise rescues neuroinflammation, the ratio of reactive microglia was determined by analyzing expression of IBA-1/COX-2. All tests were quantified in the CA1, CA2, and CA3 regions, both dorsal and ventral, of the hippocampus. Expression of NPY was higher in SED housing ($p=0.019$), and higher in the ventral region ($p=0.002$). It was also found that expression of NPY was higher in EXMD mice than EXSW mice ($p=0.001$). The CA2 region has slightly lower expression of NPY than the CA3 region ($p=0.018$). There was a significant main effect in housing by treatment as BDNF was higher in EX mice than SW ($p=0.023$). The expression of both IBA-1 and COX-2 was significantly higher in SW mice than MD mice regardless of housing ($p=0.006,0.009$). CA2 is also more significantly impacted by MD, as EXSW show lower expression of IBA-1/COX-2 and NPY than SEDSW except in the CA2. These data show that MD produces significant chronic impacts on the expression of resiliency and inflammatory factors in the hippocampus, and that exercise rescues some of these toxic effects. Funding: Schapiro Undergraduate Research Fellowship.

Prefrontal-amygdala circuits regulating cue-guided risk/reward decision-making.

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Real-world decisions often encompass uncertainty. While safe choices guarantee wins, more profitable outcomes commonly necessitate risk. Evaluation of risk/reward trade-offs can be studied with rodent models of probabilistic discounting. Here, an animal decides between a small/certain reward and a large/risky reward that's delivered at varying likelihoods. Profitable choice relies on the animalâ€™s ability to shift bias between safe and risky choices as reward probabilities change, a process thought to be mediated by the prefrontal cortex. Pharmacological inactivation of the prelimbic region (PL) of the medial prefrontal cortex attenuates this ability, resulting in increased risky choice in unfavourable conditions, and decreased risky choice in favourable conditions. The PL shares reciprocal connections with the basolateral amygdala (BLA) and research examining PL-BLA signalling in probabilistic discounting has predominantly focused on paradigms where reward probabilities are informed by the animal's intrinsic recognition of odds through trial-and-error. In real life, decisions are often informed by extrinsic cues. To address this, we selectively disrupted top-down and bottom-up PL-BLA circuits in a cue-guided probabilistic decision-making task. Rats were infected with the hM4D(Gi) DREADD receptor in either the PL or BLA. The DREADD ligand, clozapine-N-oxide, was then locally infused to disrupt PL>BLA or BLA>PL communication. Decision-making was assessed using the "Blackjack" task. Rats were given the choice between pressing a safe lever for a small/certain reward, and a risky lever for a large reward delivered at good (50%) or poor (12.5%) odds. Rats were informed of the odds by an auditory tone. Preliminary data indicate that chemogenetically silencing either the descending PL>BLA or ascending BLA>PL pathway decreases risky choice on good-odds trials. Neither manipulation reliably altered decision-making on poor-odds trials and no sex differences were observed. These findings suggest that both top-down and bottom-up PL-BLA signalling promote risky choices when conditions, as informed by external cues, are advantageous. This further highlights the contribution of prefrontal-amygdala circuitry in adaptive risky decision-making.

Differential effects of short-term social isolation on anxiety and cognition in adult and aging zebrafish (Danio rerio).

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Humans are inherently social, and it has been proposed that our social requirements are what set us apart from other species. These social relationships have a significant impact upon health through behavioural and psychological pathways as well as physiological. For example, the enforced isolation placed upon the global population caused by the SARS-CoV-19 (COVID-19) pandemic has had a deteriorating impact upon mental health with an approximate increase of 25-28% in anxiety and major depressive disorders globally. Zebrafish are used in social behaviour studies because of their innate shoaling behaviour and are a validated model for ageing-related biological and cognitive changes. The impact of social isolation on larval and adult zebrafish has been previously investigated; however, alterations in the social environment and their impact upon ageing fish remain unknown. Here, we examined the impact of social isolation upon both adult and ageing populations. We investigated the effects of short-term social isolation (lasting two weeks) on anxiety, working memory and cognitive flexibility in adult and aging fish using the novel tank (NTT) and free-movement pattern (FMP) Y-maze behavioural tests. The NTT results showed no locomotor changes following social isolation; however, isolated aging fish had increased anxiety-like responses, assessed by the top zone latency, compared to the aging control group. This effect was not observed in the isolated adult fish. There were no working memory changes following social isolation on both age groups, analysed using the FMP Y-maze. However, isolated aging fish made more repetitions and fewer alterations compared to their control contermarks over a one-hour recording period, which suggests that isolation impacts cognitive flexibility in aging but not adult fish. Our findings indicate that social deprivation has differing and notable impacts upon ageing and adult zebrafish populations with increased anxiety and altered cognition after just two weeks of isolation in the ageing group. NA is funded by a Faculty of Science studentship from the University of Portsmouth. CH is funded by Defence Science and Technology Laboratories (DSTL).

A corticothalamic circuit exhibits sex-specific regulation of sociability.

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Converging evidence from human, non-human primates and rodent studies point to the prefrontal cortex (PFC) as a central hub of the social brain. Within the PFC, enhancing the balance of excitation to inhibition is known to induce sociability deficits, but the neural circuit elements underlying this effect have remained poorly understood. In our study, we tested the contribution of neural connections from the PFC to the posterior paraventricular thalamus (pPVT) in regulating sociability in mice. Using a chemogenetic approach, we found that acute activation of PFC-pPVT neurons abolishes sociability without affecting locomotor or anxiety-like behavior. Moreover, this effect was specific to male mice. We next performed optical recordings of bulk calcium signals from PFC-pPVT neurons while mice engaged in social interaction or explored a novel object. In the male mice, we found that PFC-pPVT neurons showed a sharp reduction in activity during the first interaction with a conspecific compared to a novel object. In comparison, PFC-pPVT neurons in female mice did not show any relevant changes from baseline activity during interaction with a novel mouse or novel object. We are now using optogenetics PFC axons in the pPVT precisely time-locked to the start of social interaction to see if we can alter social interaction with more spatiotemporal control. Altogether, these results identify a novel, sex-specific role for the PFC-pPVT circuit in regulating sociability. Our results also identify, for the first time, a PFC neural circuit that may be inhibited during social interaction. A mechanistic understanding of brain activity during social interaction will help develop better biomarkers for symptomology and enhance treatment options for social deficits. This work was supported by the Drexel University College of Medicineâ€™s Dean Fellowship to NR Mack and the PA CURE Grant to WJ Gao.

Emergence of individual personality traits in mice living in same sex colonies from weaning: social behaviors, acoustic communication and motivation profiles.

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Origin of individual variability has not yet been fully defined in pathological or in healthy states despite its impact on cognition. We expect variability to be promoted by early life social interaction and, therefore, that a more naturalistic environment offering more various stimulants will favor the emergence of social variation and of individual profiles. Our aim was to study individual behavioral variability regarding social behaviors. In a group of healthy adolescent animals living in a small stable colony (12 same sex mice), we assessed the range of behavioral variation for each individual over time, as well as the differences between individuals that could lead to specific profiles. We propose that some behaviors -within the social repertoire- might change throughout development, whereas some others might be stable, thus reflecting individual profile. We focused in particular on housing conditions to mimic a more naturalistic environment that would allow animals to develop a large behavioral repertoire and maximize behavioral variability detection. Some studies developed, among other things, an Â« enriched Â» environment with bigger spaces, new objects and conspecifics but limited their impact on the animalâ€™s development by only studying it at adulthood, or within a restricted period of time. Therefore, we expected to evaluate the influence of an enriched environment compared to standard housing conditions on mice behavior from adolescence to adulthood. For that, we evaluated how an enriched environment influences individual differences in reward preference, social interactions, ultrasonic vocalizations or social motivation. We further investigated gender effects. We expect this work to increase our knowledge about the development of social profiles in mice. We shall also get information about the influence of a naturalistic environment and of gender on social and communication behaviors, and eventually on the development of social profiles.

Basolateral amygdala-striatal projections contribute to allow stress to accelerate habit formation.

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Goal-directed behavioral control is when one considers the consequences of their action before making the choice to do it. Habits are reflexive behaviors that are executed based on past success without forethought about future consequences. Habits allow efficient execution of routine actions and are normally adaptive. However, chronic stress can accelerate the formation of maladaptive habits. Our goal was to identify the neural pathways responsible for this. The dorsomedial striatum (DMS) is critical for the learning supporting goal-directed actions. It receives a direct projection from the basolateral amygdala (BLA), a region also important for goal-directed learning and highly sensitive to stress. We hypothesized that stress might attenuate activity in BLA-DMS projections to accelerate habit formation. To test this, we coupled fiber photometry calcium imaging and chemogenetic manipulation of BLA-DMS projections with an instrumental learning task designed to diagnose goal-directed v. habit behavioral control strategy in chronically stressed and control mice. Our preliminary results show the BLA-DMS pathway is active during instrumental learning and that enhancing this activity in stressed mice can prevent stress from accelerating habit formation. These data have important implications for conditions characterized by both stress and maladaptive habits. This work has been funded by NIH R01DA046679 (KW), NIH T32DA24635 (JG), NIH TL4GM118977 (NP).

Endocannabinoids influence the neural substrates of interval timing in the nucleus accumbens.

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Cannabinoids disrupt timing by interfering with dedicated brain timing circuits. The ability to perceive and respond to temporally relevant information in the environment is critical for adaptive survival, and corticostriatal circuits play a central role in timing behavior. Our previous work demonstrated that phasic dopamine release in the nucleus accumbens (NAc) encodes interval timing and that CB1 receptor activation accelerates the perception of time and shifts temporally-engendered patterns of phasic dopamine release. METHODS: Using in vivo optogenetics and neuronal ensemble recordings, we examined how endocannabinoid signaling orchestrates timing-mediated NAc network dynamics in male mice. RESULTS: We found that interval timing was encoded by bidirectional ramping activity of NAc ensembles and progressive increases in gamma frequency power of the local field potential. Increasing levels of the endocannabinoid 2-AG via the MAGL inhibitor JZL184 (18 mg/kg, ip) resulted in an acceleration of time estimation and attenuation of interval encoding in a CB1 receptor-dependent manner. Additionally, endocannabinoid-mediated disruptions in interval timing were occluded by optically-driven NAc network oscillations at gamma frequencies. CONCLUSIONS: These results reveal a significant role for endocannabinoids in the accumbal network dynamics that guide timing behavior and may have important implications for the use of pharmacotherapies targeting the endocannabinoid system and for the recreational use of plant-based and synthetic cannabinoids. Funding Acknowledgement: NIDA grant K99 DA047419 (NEZ).

Neuronal transcriptomic and epigenomic signatures of early-life adversity and exercise underlie modulations to cognitive function.

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Adverse childhood experiences are increasingly recognized as having long-term impacts on pediatric cognitive health. Interventions are needed to offset the negative consequences of early-life adversity (ELA) on later-life cognition. Rodent models can be used to identify targetable mechanisms to offset the cognitive consequences of ELA. We developed a mouse model of early-life exercise (ELE) and discovered that ELE has lasting effects on hippocampal memory and synaptic plasticity. We aim to apply post-hoc ELE to prevent ELA-induced memory deficits. Methods: We developed the Emx1-NuTRAP transgenic mouse for paired transcriptome and epigenome sequencing from hippocampal neurons. During postnatal days (P) 2-9, Emx1-NuTRAP mice were placed in limited bedding and nesting (LBN) cages to model ELA. A subset of ELA mice underwent ELE during P21-41. We isolated dorsal hippocampi from a subset of mice at P21 or P42 for mass spectrometry analysis of histone modifications. Young adult mice (P60+) underwent behavior tasks to assess spatial memory and anxiety-like behavior. Middle-aged mice (10-14 month) were tested in the objects in updated locations (OUL) task. Following OUL, we isolated dorsal hippocampi for sequencing to evaluate molecular targets of memory reconsolidation. Results: ELA exposure did not significantly reduce mouse running distances during ELE. ELA, with or without ELE, does not provoke anxiety-like behavior differences, and all mice had similar performance in hippocampal short- and long-term memory tasks in young adulthood. Mass spec revealed differences in the methylation of histone variants of H3K27 and H3K36 between ELA and ELE. Conclusion: We have established working models of LBN and ELE paradigms using Emx1-NuTRAP mice. With pending OUL results and sequencing in middle-aged mice, we aim to identify memory impairments after ELA, and whether ELE can offset the consequences of ELA. Funding: Robert Wood Johnson Foundation Amos Award, Conte Center Seed Grant, Child Neurology Foundation.

Circuit-specific chemogenetic modulation of working memory in aged rhesus monkeys

Upright Nicholas 1, Elorette Catherine 1, Fujimoto Atsushi 1, Croxson Paula 1, Russ Brian 1, Rudebeck Peter 1, Baxter Mark 1. 1 Nash Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY. Age-related deficits in working memory, attention, and other executive functions have been well characterized in rodents, nonhuman primates, and humans. Pharmaceutical drugs or more invasive treatments, such as deep brain stimulation, have been developed as potential therapies for those individuals with pathological and nonpathological forms of age-related cognitive impairment. However, it has not been shown whether a circuit-specific manipulation of a neuromodulatory system may improve cognitive performance. Prior to transduction, we investigated working memory performance in the spatial delayed response task in aged macaques after intramuscular injection or oral administration of the DREADD actuator, deschloroclozapine (DCZ). For injections, monkeys received 0.1 mg/kg DCZ and for oral administration each subject received three doses of DCZ: 0.1 mg/kg, 0.3 mg/kg, and 1.0 mg/kg. One monkey, Case C, showing particularly high levels of performance was also tested with the nonselective muscarinic antagonist, scopolamine. Following preoperative testing, we used a dual-viral combinatorial approach to precisely target projections from the nucleus basalis of Meynert to the dorsolateral prefrontal cortex and transduce excitatory hM3D-Gq-coupled DREADDs (designer receptors exclusively activated by designer drugs). We are currently testing whether activation of this circuit and modulation of a dominantly cholinergic system could ameliorate age-related working memory deficits in a delayed response task. Aged monkeys took significantly longer to learn the delayed response task compared to younger counterparts. Aged monkeys were also significantly impaired in the variable delay paradigm of the task compared to young monkeys. Prior to DREADD transduction, aged monkeys showed no significant differences in working memory function after DCZ compared to that after vehicle, both following intramuscular injection or oral administration. Given the importance of acetylcholine in these prefrontal-mediated functions, these experiments may provide a novel potential neurotherapeutic approach for circuit-specific treatment of those cognitive impairments seen in aging and disease that result from deficits in cholinergic neuromodulation.

The role of the BNST in the regulation of natural reward consummation

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The bed nucleus of the stria terminalis (BNST) is involved in the regulation of reward and aversion, self-administration of drugs of abuse, and copulation. Here, we investigated the involvement of the BNST in self-administration of sucrose, as well as in different phases of sexual behavior. We hypothesized that the BNST influences engagement in these behaviors depending on the internal state of the animal. AAV5-CaMKIIa-GFP, -Gq, or -Gi DREADDs were bilaterally injected into the BNST of two cohorts of adult male rats (n = 9-12 per group per cohort). Cohort 1 was trained to lever press for sucrose pellets under a fixed ratio 1 (FR1) and progressive ratio (PR) schedule of reinforcement, and assessed for number of obtained rewards following clozapine-N-oxide (CNO) versus vehicle administration. We next tested whether food restriction preceding PR testing influenced effects of CNO. Cohort 2 was behaviorally assessed in a sexual incentive motivation test and a copulation test upon administration of CNO and vehicle, after normal social housing as well as after one week of single-housing. Both stimulating and silencing the BNST increased self-administration of sucrose pellets under FR1, but not under PR. Food restriction preceding PR testing did not influence the number of obtained rewards upon CNO administration. Sexual incentive motivation was not affected by silencing or stimulating the BNST, and was not influenced by prior social deprivation. Preliminary results indicate a decrease in achieved ejaculations upon BNST silencing in the copulation test. We conclude that the BNST is involved in the regulation of consummation of natural rewards; reduced self-administration of sucrose in a minimal effort regimen, as well as reduced ejaculatory efficiency. In contrast, we found no evidence of BNST involvement in motivational aspects of these behaviors, as our intervention did not influence the motivation to work for sucrose, nor sexual incentive motivation, regardless of the internal state of the animal.

Chronic early-life resource deprivation disrupts the landscape and function of cortical inhibitory neurons

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Nearly half of all children in the United States are exposed to adverse childhood experiences, with up to 20% experiencing chronic exposure to multiple stressors. Chronic exposure to early life stress (ELS) has dramatic, life-long consequences, tripling the risk of dementia, quadrupling the risk of depression and increasing the risk of suicide 30-fold. To study the impact of chronic ELS in a mechanistic manner, we developed a mouse model of ELS in which wild type Swiss Webster mice are deprived of nesting and bedding material from postnatal day 2 into adulthood. Adult male mice exposed to cLNB stress displayed higher levels of anxiety, hyperactivity, and sociability relative to control mice. To determine the neural basis of these behavioral disruptions, we chose to focus on cortical inhibitory interneurons, as this cell population is actively undergoing migration and maturation during the initiation of the chronic stress paradigm. We assessed the distribution of parvalbumin interneurons across multiple brain regions using whole brain imaging. cLNB stress dramatically altered the density of PV neurons (PVNs) in the prefrontal cortex. Transcriptomic analysis revealed that stress-exposed prefrontal PVNs up-regulate their metabolic and mitochondrial activity. Chemogenetic activation of prefrontal PVNs rescued anxiety deficits in cLNB exposed mice. Overall, this work confirms that cLNB stress induces changes in the landscape and function of cortical PVNs, and that this cell-type may be a key driver of neurobehavioral changes induced by stress experienced early in life.

A novel assessment of rule-learning in mice using operant touch screen boxes.

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Historically, the development of valid and reliable methods for assessing higher order cognitive ability (e.g., rule learning and transfer) has been tricky in rodent models. One barrier is verifying that subjects are actually using cognitive processes assumed by investigators, versus unexpected approaches to solve the task. Although rats have shown marginal evidence of being able to learn and transfer information from one set to another (e.g., attentional set shifting), mice have shown limited abilities in this domain. Yet the exploding use of engineered mouse models to study genetic disorders characterized by cognitive disruption would benefit tremendously from the inclusion of such a task in mouse phenotyping batteries. For the current experiment, we sought to develop a task that would require mice to learn a visual discrimination task of increasing complexity, following fixed parameters or "rules." Mice would then be asked to apply the remembered rules to a novel (new) image set. Twenty-eight (28) wild-type male c57 mice performed the initial visual discrimination, which was conducted in Bussey-Saksida touchscreen operant boxes. We used 2 different image sets, counterbalanced for the image set each group received first. Results showed that mice were able to quickly learn the first image set, and could learn the "rule" based on performance curves that were significantly better than initial learning when image sets became more complex. They could also remember this information many weeks later. However, the mice appeared unable to transfer the rule to a new set of stimuli. Specifically, they showed visual discrimination curves for the new image set that was no better than the first (naÃ¯ve) round of learning. We continue to revise this task to optimize stimulus parameters and maximize task sensitivity, hoping to better tap these important cognitive measures in mice. Work supported by the University of Connecticut Institute of Brain and Behavioral Sciences (IBACS), and the Murine Behavioral Neurogenetics Facility (MBNF).

Cannabidiol accelerates the development of tolerance to the analgesic effects of oxycodone but not morphine: a potential drug-drug interaction.

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Opioids are the primary treatment for severe pain, postoperative pain relief and chronic pain. However, repeated opioid use results in tolerance to their analgesic properties which significantly limits their long-term efficacy. Tolerance can also lead to escalation of intake, which contributes to the development of an opioid use disorder. As a result, there has been an emerging interest in the use of medicinal cannabis alongside opioids to enhance the analgesic efficacy of opioids, with nearly one quarter of people using opioids for chronic non-cancer pain reporting also using medicinal cannabis. We examined the effects of one of the major cannabinoids found in the majority of medicinal cannabis products, cannabidiol (CBD), on tolerance to the analgesic effects of opioids. To model opioid tolerance in male and female mice, we administered oxycodone (10 mg/kg) or morphine (15 mg/kg), twice daily over 5 days, followed by tests of thermal pain sensation. CBD was administered prior to each opioid injection, excluding test day. Unexpectedly, CBD co-administration accelerated the development of tolerance to the analgesic effects of oxycodone but had no effect on the development of tolerance to morphine. CBD is known to inhibit CYP2D6 and CYP3A4 enzymes which are involved in the metabolism of oxycodone, but not morphine. Therefore, one possibility is that CBD interfered with the metabolism of oxycodone, increasing exposure to oxycodone, and thereby exacerbating the development of tolerance to its analgesic effects. We are now conducting molecular studies to determine whether this interaction between CBD and oxycodone is reflected in the neural substrates which mediate opioid analgesic tolerance and conducting CYP interaction studies to further probe the possibility that these findings are driven by a drug-drug interaction. These data suggest combining CBD (now legal and easily accessible in many countries) and oxycodone (the most prescribed opioid) may be contraindicated.

Role of Dopamine Neurons in Familiarity

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It is well established that dopamine (DA) neurons in the ventral midbrain signal novelty byincreasing their bursting activity and decreasing activity after repeated stimulus presentations. This provides a physiological signature that a stimulus has become familiar. Here, we hypothesized that decreasing DA neuron activity is sufficient to drive rapid familiarization. To test this hypothesis, we used a Novel Object Recognition (NOR) paradigm where mice were presented with two identical objects (A, A) during a familiarization session, then presented with a new object and one previously seen object (A, B) in a subsequent session. Time spent exploring the new object provides an index of recognition for the familiar object. Further, this exploration time is dependent on the amount of pre-exposure to the familiar objects. We found that one familiarization session is not sufficient to increase exploration of a novel object. We hypothesized that the equal attention allocated to both stimuli during NOR session is likely driven by the fact that DA neuron activity did not decrease during the one familiarization session; consequently, decreasing DA activity during familiarization should improve novelty discrimination.To test this hypothesis, we used chemogenetics to inhibit DA neurons in the ventral tegmental area (VTA). TH-flp mice received injections of an AAV8 flp-dependent hM4Di. We then stimulated hM4Di receptors via i.p. CNO (1mg/kg) and found that inhibiting DA neurons during familiarization increased subsequent novel object exploration. To confirm these results were due to an effect on familiarity, we inhibited DA neurons after the familiarization session, and observed no improvement in NOR. These results suggest that suppressing DA neuron activity enhances familiarity recognition. Ongoing experiments suggest that this DA-dependent effect on familiarity may be due to a facilitation of object-context association. R21 MH123926

Ventral hippocampus is required for updating action-outcome association through context-outcome learning.

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The ability to select appropriate actions according to the situation is important for survival. The neurocognitive bases of action selection can be studied using instrumental conditioning paradigms. In these paradigms, animals learn to perform different actions (e.g., lever presses) to earn distinct outcomes (e.g., food rewards). Thus, the animal needs to encode both the causal relationship that exists between the performance of the action and the delivery of the outcome and the incentive or motivational value of the outcome. Such â€œgoal-directedâ€• actions are highly adaptive as they are sensitive to subsequent changes in both the action-outcome relationship as well as changes in outcome values. Decades of research has improved our understanding of the broad psychological aspects and underlying neuronal substrates that support such behavior. Yet, to date the influence of the environmental context on goal-directed action remains poorly understood. Here, we studied whether goal-directed behavior relies on activity in the ventral hippocampus (vHPC), a structure well known for its role in the contextual regulation of other forms of associative learning. We first assessed the effect of pre-training vHPC lesions on outcome devaluation, a task designed to assess whether an action is sensitive to changes in outcome value. We found that inhibition of vHPC left outcome devaluation intact. We then assessed the effect of vHPC inhibition on contingency degradation, which requires the animal to learn that the environmental context (and not the action) is now the best predictor of outcome delivery. We showed that rats with vHPC inhibition were unable to readily adapt their behavior when the causal relationship between the action and the outcome was disrupted, and the context became the best predictor of reward. This suggests that the vHPC may be required to form context-outcome relationships to guide adaptive behavior and appropriate action selection. This work was supported by the Brain & Behavior Research Foundation (NARSAD Young Investigator Grant ID: 27402), the French National Agency for Scientific Research (CoCoChoice ANR-19-CE37-0004-07) and a PhD fellowship from the French Ministry of Higher Education, Research and Innovation.

Behavioural changes in young adult pre-symptomatic C9orf72, MAPT and GRN mutation carriers: A GENFI study

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Frontotemporal dementia (FTD) is the second most common young-onset neurodegenerative dementia, with disease onset typically occurring in the 5th or 6th decade of life. However, symptoms can start years before clinical diagnostic criteria are met, and recent findings suggest that some forms of genetic FTD may have neurodevelopmental effects. Investigation of behavioural symptoms and cognitive performance in young, pre-symptomatic mutation carriers and their familial non-carriers may further indicate whether and which forms of genetic FTD may have neurodevelopmental effects. Participants included 85 young adults, ages 18-29 years, enrolled in the Genetic Frontotemporal Dementia Initiative (GENFI) multi-centre cohort study, with known pathogenic mutations in the GRN or MAPT genes or with a pathogenic expansion in the C9orf72 gene. Participants completed a battery of cognitive tasks and their informants completed symptom and behavioural ratings. Several significant differences in task performance between carriers and non-carriers were observed in each of the three mutation groups. On Block Design, a measure of spatial construction and motor skill, male C9orf72 carriers scores deteriorated as age increased, while performance in male non-carriers and female carriers and non-carriers were comparable and stable over the age range (F(1,10)=5.21, p<0.05). On a verbal phonemic fluency task, MAPT mutation carriers generated more F-, A-, and S- words than non-carriers (F(1,6)=30.62, p<0.01). Additionally, on an informant-based measure of symptoms, fewer symptoms were reported for MAPT carriers than non-carriers (F(1,13)=5.23, p<0.05). In GRN mutation carriers, a significant interaction effect between carrier status and age was found on the verbal phonemic fluency task (F(1,16)=4.876, p<0.05), with a trend towards better performance in young (<26.05 years) non-carriers compared to young carriers (p=0.065). These novel findings suggest potential neurodevelopmental consequences of FTD mutations with distinct cognitive profiles that could ultimately serve to inform future interventions for at-risk individuals.

Cognitive and social behavioral outcomes in premature infants following neonatal adenosine antagonist treatment: Influence of drug timing, pre-existing prenatal inflammation, and sex

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Caffeine and theophylline are adenosine antagonists that are commonly used as neonatal respiratory stimulants for apnea of prematurity and/or transition from ventilation. Evidence suggests that caffeine may also act as a neuroprotectant against hypoxic-ischemic brain injury. Hypoxia-ischemia (HI), or the loss of blood supply and/or oxygenation, is very common in the preterm brain following episodes caused by cardiopulmonary immaturity and failure. Clinical results show that giving caffeine within the first 3 days of life rather than later leads to better cognitive outcomes at 18 months and 24 months. However, these studies do not take into account several other factors that could influence cognitive outcomes, such as sex and other prenatal conditions (preeclampsia, chorioamnionitis (chorio), and magnesium sulfate treatment). For the current study, medical record data was taken for infants born 23-30 weeks gestational age between the years of 1991 and 2017 who were treated with caffeine or theophylline. Infants who received treatment within the first 48 hours of life were compared to infants who received methylxanthines after 48 hours, using subsequent cognitive outcomes obtained in follow-up assessments as an index of efficacy. Infants were further split into groups based on sex and comorbid conditions, for comparison. Results showed a significant benefit when adenosine antagonists were provided<48 hours after birth as compared to later, and these effects were particularly evident for language and social measures. Additional results addressing interactions between adenosine treatment and perinatal inflammation, as well as sex, will be presented. Our results indicate that earlier (immediate) treatment may be particularly beneficial for long-term outcomes, even in the absence of neurologic injury. We will discuss clinical implications for more aggressive use of caffeine in preterm infants, as well as clinical recommendations to optimize outcomes.

Chronic effects of cannabis on cognition in aging.

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Older adults are the fastest-growing group of cannabis users in the US. Cannabis and its constituents such as delta-9-tetrahydrocannabinol (THC), the major psychoactive component of cannabis, generally impair cognitive performance in young adults. Given that many older adults suffer from age-related cognitive impairments, however, it is important to understand how cannabis and cannabinoids affect cognition in this age group. To address this issue, we conducted an initial study in rats to evaluate the effects of chronic oral THC self-administration on working memory. Young adult (5 months) and aged (23 months) Fischer 344 x Brown Norway F1 hybrid rats of both sexes were trained on a delayed response working memory task in operant test chambers, in which they had to remember the left/right position of a response lever over short delays (0-24 s) to earn food rewards. Upon reaching stable performance, rats were given 6 weeks of daily 1-hour access to either plain gelatin or gelatin containing 1 mg/kg THC in their home cage in the afternoons, while testing in the working memory task continued in the mornings. As expected, among rats that consumed plain (control) gelatin, aged rats performed worse than young, particularly at longer retention delays. In the young group, rats that consumed THC gelatin performed worse than rats that consumed plain gelatin. In the aged group, however, rats that consumed THC gelatin performed better than rats that consumed plain gelatin. These findings suggest that under some conditions (poor baseline performance and/or advanced age), cannabis and cannabinoids may provide cognitive benefits, even when consumed chronically. Supported by NIH RF1AG072714 and T32AG061892, Florida Department of Health 21A11, and the McKnight Brain Research Foundation

Involvement of an oxytocinergic hypothalamic-striatal pathway in the regulation of juvenile social play behavior

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Social play is a highly motivated and rewarding behavior displayed primarily by juveniles of many mammalian species. While exposure to social play aids in the development of social competence, deficits in social play, as seen in autistic children, may contribute to life-long impairments in social behaviors. The oxytocin (OXT) system is considered a potential therapeutic to improve social interaction in autistic individuals. However, little is known about the role of OXT in social play. To fill this gap, we first determined the involvement of OXT cell populations in the paraventricular nucleus of the hypothalamus (PVN) and supraoptic nucleus (SON) in social play. To achieve this, an excitatory DREADD construct under the control of the OXT promoter was infused into either the PVN or SON of 26-day-old juvenile male and female Wistar rats. One week later, social play behavior was assessed over two trials, in which either clozapine-N-oxide or saline was administered prior to testing. A significant sex x drug interaction was found in the PVN, in which chemogenetic stimulation of PVNOXT cells decreased social play duration in males and increased social play duration in females. Chemogenetic stimulation of SONOXT cells did not alter social play behavior but increased social investigation in both sexes. These findings demonstrate the potential for distinct roles of the PVNOXT and SONOXT systems in the modulation of social behavior in juvenile rats. Because the PVNOXT system selectively modulated social play in a sex-specific manner, we next examined the involvement of downstream targets of the PVNOXT neurons. Using both anterograde and retrograde tracing techniques, we demonstrated that PVNOXT fibers terminated in the nucleus accumbens (NAc), which is known for its involvement in social play. Experiments are underway to determine whether chemogenetic stimulation of the PVNOXT to NAc pathway regulates social play behavior and if it does so sex-specifically. Taken together, these findings will provide insights into the potential need for sex-specific use of OXT-based therapeutics to improve social play engagement in autistic children.NIMH R01MH102456

Self-administration acquisition rate predicts locomotor sensitivity to cocaine in male rats

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Most individuals who initiate cocaine use do not go on to develop a cocaine use disorder. Differences in susceptibility to cocaine use begin to emerge after initial exposure: some users discontinue cocaine self-administration after a single exposure, some use intermittently over an extended period of time, and others promptly develop a compulsive binge pattern. In rodents, individual differences in cocaine self-administration also emerge early on: some rats rapidly acquire a cocaine self-administration behavioral task, while others require multiple training sessions. Whether individual differences in acquisition rate reflect capacity to acquire the behavior, or are related to differences in characteristics about cocaine that arise after maintained use remains unclear. Here, we attempt to determine whether rate of cocaine acquisition predicts subsequent cocaine self-administration behavior, locomotor sensitivity to cocaine, motivation for cocaine, or cocaine-seeking following two weeks of abstinence. We first evaluated 14 male Sprague-Dawley rats in an open field test to gauge basal locomotion and anxiety-like behavior. Next, we subjected rats to daily 3h cocaine (0.75mg/kg/infusion) self-administration sessions until rats met acquisition criteria (≥30 active lever presses with ≥75% responding on the active lever in one session). Upon meeting acquisition criteria, we trained rats for 10 additional sessions to ensure all had equal opportunity to self-administer cocaine. Following self-administration training, we measured performance in a progressive ratio test, locomotor sensitivity to cocaine, and lever pressing in a non-reinforced cocaine seeking test after 2w of forced abstinence. Rats were divided into Early and Late Learner groups based on their number of sessions taken to meet acquisition criteria by median-split analysis. Early Learners exhibited significantly less locomotion following an intraperitoneal injection of cocaine than Late Learners, but groups did not differ in any other behavioral parameter examined. These results indicate that cocaine self-administration acquisition rate is not predictive of subsequent motivation for cocaine or cocaine intake, but rather may be linked to physiological factors that predispose rats to learn an operant task, such as cocaine sensitivity.

Characterization of resident and intruder interactions in the social defeat model of stress.

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Major depressive disorder (MDD) is a leading cause of disability worldwide, and is characterized by persistent and prolonged despair and anhedonia. Although multiple biological and environmental factors contribute, it is well-established that social stressors play an important role in the etiology of MDD. Accordingly, social stress has been modeled in preclinical studies using the social defeat paradigm in rodents. In this model, a naÃ¨ve male â€œintruderâ€• mouse or rat is confined in the home cage of a â€œresidentâ€• male conspecific, that has been trained to exhibit territorial dominance. Patterns of dominant and submissive behaviors have been examined in mice. However, changes in these behaviors have not been thoroughly characterized across repeated resident training and testing days in rats. We are characterizing the time course of changes in dominance and submissive behaviors over time in both the resident and intruder rats, including potential correlations between the submissive behaviors in the intruders, and the intensity of dominance exhibited by the residents. In addition, we are examining the contribution of pre-existing dominance hierarchies to the behavioral profiles of the intruder rats when they are placed into defeat sessions with the trained residents. Retired breeder male Long-Evans rats were individually housed in oversized polycarbonate cages, and naÃ¨ve young adult (6-7 weeks) Sprague-Dawley rats were pair housed in standard shoebox cages. Interactions between the paired Sprague-Dawley rats were evaluated in their home cages. Then, on each of 8 consecutive training days a Sprague-Dawley intruder was placed into the cage of a resident Long-Evans rat, so each resident was exposed to a different intruder each day. Dominance and submissive behaviors were quantified. Preliminary examinations reveal that the average latency to defeat an intruder decreased over the 8 training days, indicating that the territorial dominance of the residents increased with experience in the social defeat model. Additional parameters are under investigation. This project is funded by the UF Informatics Institute Seed Fund 2021.

Prenatal alcohol exposure alters behavior and power in translational neurophysiological signals during rodent touchscreen tasks

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Although it is well established that alcohol consumption during pregnancy has a life-long impact on offspring, Fetal Alcohol Spectrum Disorders (FASD) remain the most common neurodevelopmental syndrome. Poor reporting of alcohol consumption during gestation and underdiagnoses of FASD requires novel diagnostic tools and improved behavioral measures between clinical and preclinical models to increase translation between species. FASD patients struggle with cognitive control utilizing a 5-Choice Continuous Performance Task (5C-CPT). 5C-CPT can be easily integrated with EEG in humans and EEG-like recordings in mice. Here, we incorporated a touchscreen 5C-CPT with EEG-like recording in a rodent prenatal alcohol exposure (PAE) model. Male and female mice were obtained from the NMARC drinking-in-the-dark model (10% EtOH with 0.066% saccharine for 4hrs/day throughout gestation; BAC: ~90mg/dL; controls=0.066% sweetened water, â€œSACâ€•). Mice first trained to touch 1 target stimuli rapidly and accurately before stereotactic surgery for skull screws targeting medial prefrontal, parietal, and motor cortices, with a ground over the cerebellum. After recovery and reminder to criterion, nontarget trials (5 stimuli presented; withholding of response rewarded) were added at a 2:1 ratio for 5 days followed by recording at a 5:1 ratio for 12 days. Mice also tested and recorded 1 day for physical effort on a progressive ratio breakpoint procedure wherein they had to touch a single stimuli with increasing responses in order to receive reward. . Lastly, mice recorded for 5 days on PLT wherein the probability of reward differed for the target and nontarget image. We found that PAE impaired withholding response to nontargets during 5C-CPT and increased impulsivity on the PRBP, these deficits in behavior tracked with decreases in power in relevant a priori regions of interest in the EEG-like signal. These results utilizing EEG-like recording suggest that alterations in cortical activity can be used as a potential biomarker of PAE. This work was supported by the NIAAA grants 2P50AA022534-06, 1R01AA025652-01 and 5T32AA014127e13

The sex specific effects of acute ketamine treatment on neural and behavioral outcomes following early life adversity.

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Early life adversity (ELA) significantly increases an individual's risk of developing various psychiatric disorders, including anxiety and depression. However, despite the high prevalence and complexity of these disorders, the treatment options are limited. Considering the increased instance of mood disorders in females, sex is an important, but often overlooked, variable to consider when developing and assessing possible treatments. Ketamine has been increasingly used with marked success for treatment resistant depression; however, the mechanisms behind its anti-depressant actions remain largely unknown. A protein whose dysregulation appear associated with anxiety and depression is parvalbumin (PV), a fast-spiking calcium binding protein important for orchestrating neuronal activity. Additionally, PV appears to be sensitive to early life experiences, which suggests that it may play a role in the psychiatric outcomes associated with ELA. Given that previous research has found an interaction between ketamine and PV, we propose that ketamine may return PV levels back to typical levels, thus explaining its anxiolytic and antidepressant effect, and that this may be sex specific. Here, we identify potential mechanisms behind ketamine as a treatment for anxiety and depression in a translational rodent model, as well as considering the role of sex as a biological variable in behavioral outcomes following ELA exposure. Rats underwent maternal separation over the first 20 days of life and then were treated with a single therapeutic dose of ketamine (15mg/kg) in young adulthood. Following ketamine treatment, depressive anhedonic (sucrose preference) and anxiety-like (elevated zero maze and open field test) behaviors were assessed. Brain tissue samples were evaluated for PV levels in the prefrontal cortex. Here we provide a more nuanced understanding of the possible contributions of these neural markers on behavioral outcomes following treatment as a function of sex. Understanding the sex-specific molecular mechanisms behind ketamine's anxiolytic and anti-depressant effects will allow us to better treat patients with affective disorders.

Sex differences in behavior and glutamic acid decarboxylase (GAD) expression following adolescent social isolation in Long Evans rats

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Early life stressors, including social isolation, can have detrimental effects on brain development and adult behavior. The inhibitory neurotransmitter GABA modulates stress responses and is synthesized by glutamate decarboxylase (GAD). This study examined the long-term effects of adolescent social isolation on behavior and GAD expression using male and female Long Evans rats. Anxiety-like behaviors were measured using the open field test (OFT) and elevated plus maze (EPM), social interactions were assessed with a sociability task, and cognition was tested using novel object location (NOL). Overall, our findings suggest that social isolation during adolescence produced anxiogenic effects in females and reduced GABA-ergic activity in the hippocampus in both sexes. These studies have important implications given the millions of adolescents who have experienced prolonged social isolation during the COVID-19 pandemic.

Post-conditioning lesions to the perirhinal cortex does not impair fear extinction learning.

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The perirhinal cortex (PER) is a medial temporal lobe structure involved in learning and memory. The PER receives both unimodal and polymodal sensory information, which makes this region well-positioned to associate and process stimulus information. Previous research suggests that the PER supports fear-related associative learning to stimuli that require unitization across modality or time. For example, PER lesions produce deficits in fear conditioning to discontinuous auditory cues and contexts. A recent study suggested that this role of the PER may also extend to fear extinction learning. In the current study, we further explored perirhinal involved in fear extinction by asking whether excitotoxic lesions to the PER after fear conditioning would affect extinction learning to a continuous or discontinuous conditioned stimulus (CS). Thirty-eight male Spraque-Dawley rats were assigned to one of four groups based on CS type (continuous vs discontinuous) and surgery type (lesion vs sham). Animals underwent surgery three days after fear conditioning, then ten days later returned to the conditioning chamber for extinction training and extinction retrieval. Freezing behavior was recorded and analyzed offline. We predicted that the PER would be necessary for fear extinction to a discontinuous CS but not a continuous CS. Results show that animals in all groups displayed comparable increases in freezing during fear conditioning, indicative of successful acquisition. After surgery, there were no significant differences in freezing levels for PER lesioned and sham animals during extinction training to the continuous or discontinuous light CS. During extinction retrieval, there was again no significant difference between lesion and sham groups to the continuous light CS. However, there was a significant decrease in freezing level in the PER lesion compared to the sham group in the discontinuous Light CS group. Unlike a previous study that used temporary inactivation of the PER, the current study did not support the involvement of the PER in fear extinction learning. The contradictory results may indicate a compensatory mechanism when the PER is not available or alternatively may suggest that the PER has a time-limited role in fear learning. Acknowledgments: NSF Grant IOS 175111 to S.C.F.

Multiple dopamine receptor subtypes exert sex-dependent modulation of cue-guided risk-reward decision making

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The ability to integrate cues to guide efficient decision making is a central behavioral adaptation in many organisms, and disorders involving pathophysiology of the dopamine (DA) system are associated with sub-optimal decision-making. Prior research into dopamine modulation of decision-making has used probabilistic discounting tasks where internal representation of probability guide choice. Yet, real-world decision-making often involves incorporating external cues. To measure this, our group has developed a rodent assay known as the â€œBlackjack taskâ€• , requiring rats to use external cues to guide optimal decisions. Each trial involves the presentation of one of two auditory cues, followed by the extension of two levers. Rats choose between the small/certain lever (1 sugar pellet at 100% probability) and the large/risky lever (4 pellets, probabilistically). The auditory stimuli signals if the large/risky lever will have good (50%) odds or poor (12.5%) odds of delivering the large reward. Using this task, we investigated the influence of systemic DA antagonists in male and female rats. Animals were well-trained on the task and then received systemic injections of either amphetamine, D1, D2, D3, or D4 antagonists prior to testing. Previous work by our group has shown that D1 blockade reduces risky choice during probabilistic discounting guided by internal representations of reward history. In contract, similar doses of the D1 antagonist did not affect choice on the Blackjack task, whereas higher doses induced non-specific disruptions in choice. This suggests recruitment of distinct underlying decision-making circuits between the tasks. Administration of a D2 antagonist induced sex-dependent suboptimal decision making, reducing and increasing risky choice on good and poor odds trials for females and males respectively. D3 antagonists did alter choice, whereas D4 antagonists induced significant reduction in risky choice on good odds trials, but only in females. In comparison, amphetamine induced biphasic, dose-dependent changes in decision making, in that a lower dose (0.25 mg/kg) decreased risky choice on poor odds, whereas higher 0.5-1.0 mg/kg doses led to sub-optimal decision making and increased risky choice on poor odds trials. These findings highlight the importance of including subjects of both sexes, and the differential contributions of DA receptors in cue-guided decision-making.

DIFFERENT INVOLVEMENT OF ANTERIOR AND POSTERIOR PARAVENTRICULAR NUCLEUS OF THE THALAMUS IN THE DEVELOPMENT OF SIGN-TRACKING BY MICE OF TWO INBRED STRAINS

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Preclinical studies on the neurobiological determinant of individual variability can reveal mechanisms and processes responsible for susceptibility and resilience to psychopathology and differential responsivity to therapies. Comparative studies in inbred mouse strains, which have thoroughly mapped genotypes and known phenotypic differences, represent an effective method to study these complex, polygenic, and multifactorial phenotypes. Mice of the DBA/2J (D2) and C7BL/6J (B6) inbred strains develop sign tracking rather than goal-tracking in young adulthood. However, this phenotype, associated with sensitivity to incentive salience, is modulated by serotonin transmission in the prelimbic cortex (PL) in B6 but not in D2 mice. In this study, we tested the involvement of the paraventricular nucleus of the thalamus (PVT), which modulates the development of sign-tracking through its connectivity with PL. Exposure to the food-predicting cue increased c-fos expression in the anterior PVT of sign-tracking B6 mice, inhibiting c-fos expression in the same brain area as D2 mice. Moreover, whereas an excitotoxic lesion of the posterior PVT prevented the development of sign-tracking by B6 mice, in D2 mice, a lesion of the anterior PVT only produced this same effect. These results support genotype-specific differences in the brain circuits involved in the development of sign tracking. Funding: Ateneo 2018 (RG118164367FF640)

EARLY DISRUPTION OF MOTHER-PUP ATTACHMENT FOSTERS EITHER SUSCEPTIBILITY OR RESISTANCE TO DEVELOP ANXIETY/DEPRESSION PHENOTYPES IN ADULTHOOD, DEPENDING ON GENOTYPE

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Repeated cross-fostering (RCF), involving daily changing of the fostering mother from postnatal day 1 to postnatal day four and leaving the pups with the last adoptive mother until weaning, exerts sex and genotype-specific effects on adult behavioral and neural phenotypes in mice. We investigated whether RCF also influences susceptibility to the adult experience of chronic variable stress (CVS), a major determinant of risk and severity in neuropsychiatric disorders. Adult female mice from the DBA/2J (D2) and C57BL/6J(B6) inbred strains, either submitted to the RCF or left undisturbed with their biological mothers until weaning (Control: Cl), were submitted to CVS. The protocol also included forced swim (FST), tail suspension, and elevated plus maze tests, each performed once a week three times in random order. At the end of the stress protocol, mice were implanted with a microdialysis probe in the nucleus accumbens to evaluate dopamine (DA) outflow during and after a further FST. CVS-exposed mice showed increased anxiety and depressive-like phenotypes by the third week of exposure. These effects were reduced or eliminated in RCF B6 mice but increased in RCF D2 mice. Finally, CVS experience strongly impaired the recovery of baseline DA levels following FST in Cl B6 and RCF D2 mice, which showed the highest levels of depressive-like phenotypes. These results indicate an opposite genotype-specific influence of RCF on CVS-fostered behavioral and neural phenotypes. GrantFIRB 2010-RBFR10RZ0N Ateneo (RP118164336EF3FD; RM120172B7A3A801)

Whole Litter Phenotyping in a Dosing Study of Maternal Immune Activation

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Women exposed to infections during pregnancy have an increased risk of having a child with a neurodevelopmental disorder (NDD). The maternal immune response has been identified as a risk factor for NDDs using preclinical maternal immune activation (MIA) models. MIA studies using rodents often select individual animals from a litter from which to run behavior studies, which may impact the variability seen in behavioral performance. In addition, MIA studies typically only use one dosage of an immune stimulant, limiting our ability to interpret how the strength of an immune response during pregnancy can impact offspring behavior. Here, we examined the behavior of whole litters in a rat model of MIA after exposure to two different dosages of the immune stimulant lipopolysaccharide (LPS).Research Objectives: To identify behavioral differences between dosage in a rat model of maternal immune activation. Specifically, we aimed to examine early offspring communication, social behavior, anxiety, sensorimotor gating, spatial working memory and cognitive flexibility.Methods: Sprague-Dawley females were time mated and injected with either saline, 50Âµg/kg LPS, or 100 Âµg/kg LPS at gestational day 14.5. Sera was taken from the dams before and 2 hours after injections. After birth, over-large litters were culled to 10 animals each. The litters were then tested on ultrasonic vocalizations (USVs) and early developmental milestones at post-natal days (PND) 4, 8, and 12. Following weaning, litters were tested on the elevated plus maze at PND26, juvenile social dyads at PND36, spontaneous alternation on a Y-maze at PND55, and pre-pulse inhibition at PND90. After PND90, one male from each litter was chosen for the attentional set shifting task, which was designed to assess cognitive flexibility without relying on visual acuity. Results: MIA animals showed a decrease in early communication through a decrease in the number and duration of calls at PND4. MIA offspring had altered reflexes shortly after birth. Post-weaning, MIA animals spent less time in the open arms of the elevated plus maze. Different dosages of LPS at GD14.5 resulted in different behavioral phenotypes in the offspring. The level of IL-6 activation in the dam after injection correlated with the severity of these behavioral phenotypes in the offspring.

From an empty stomach to anxiolysis: molecular and behavioural sex differences in ghrelin axis

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Ghrelin, a stomach-produced hormone, is well-recognized for its role in promoting feeding by acting on the growth-hormone secretagogue receptor 1A (GHSR1A). Ghrelin’s function to ensure survival extends beyond that: its release parallels that of corticosterone, and ghrelin administration and fasting have an anxiolytic and antidepressant effect. This clearly suggests a role in stress and anxiety. To date, most studies of ghrelin's effects on anxiety have been conducted exclusively on male rodents. Here, we hypothesize that females are wired for higher ghrelin sensitivity compared to males.In line with our hypothesis, we show that female rats have higher serum levels of ghrelin and lower levels of the endogenous antagonist LEAP-2, compared to males. Additionally, females express higher levels of GHSR1A in brain areas involved in feeding and anxiety, such as the lateral hypothalamus, hippocampus, and amygdala. Moreover, overnight fasting increased GHSR1A expression in the amygdala of females, but not males. To evaluate the behavioral consequences of these molecular differences, male and female rats were tested in the elevated plus maze (EPM), open field (OF), and acoustic startle response (ASR) test after three complementary ghrelin manipulations: increased endogenous ghrelin levels through overnight fasting, systemic administration of ghrelin, or blockade of fasting-induced ghrelin signaling with a GHSR1A antagonist. We show that females exhibit a stronger anxiolytic response to fasting and ghrelin in the ASR, supporting our findings of sex differences in the ghrelin axis. Most importantly, after antagonizing ghrelin’s effects, females but not males show an anxiogenic response in the ASR, and a more pronounced anxiogenesis in the EPM and OF compared to males. Collectively, our findings suggest that female rats are wired for higher ghrelin sensitivity compared to males and consequently show stronger behavioral responses to endogenous and exogenous ghrelin manipulations. Funded by Swedish Research Council 2018-00660, Wallenberg Foundation (WCMTM).

Adenosine 3 Receptor Agonist as a Treatment for Traumatic Brain Injury

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Traumatic brain injury (TBI) often leads to reduced quality-of-life including impairments in cognitive functioning. Changes that can occur include impaired thinking, memory, and learning. Cognitive impairment (CI) poses a large public health concern as it is estimated that up to 50% of mild TBI (mTBI) survivors will develop CI and there is no FDA approved treatment. Previously, we demonstrated that administration of MRS5980, a highly selective A3AR agonist, was able to prevent the development of CI 4 weeks after mice were subjected to a weight-drop model of mTBI these results corresponded to reduced neuroinflammation. Presently, we investigated whether this beneficial cognitive effect would be preserved if treatment was delayed after injury, modeling human patients who do not seek care immediately post trauma. Mice were subjected to either sham procedure or weight-drop TBI, as described previously. Injured mice were then divided into groups that would receive vehicle or 1 mg/kg MRS5980 via I.P. injection beginning at 1h, 24h, or 72h post procedure. Sham mice received vehicle. MRS5980 or vehicle treatment continued every 48h for the duration of the study. Extensive behavioral testing was conducted 4 weeks post trauma to assess activity levels, anxiety, learning, memory, executive function, and depressive behaviors. We found no difference in activity, anxiety, or depressive behavior between groups. Learning and memory were assessed via novel object recognition (NOR) and T-maze paradigms. Learning and memory were preserved in 1h and 24h treatment groups compared to injured, vehicle treated mice. Interestingly, mice who began treatment 72h post trauma had preserved memory in the T-maze test, but not NOR. Other A3AR agonists are in clinical trials for inflammation and cancer treatment with good safety and efficacy profiles. The present study supports MRS5980 as a strong candidate therapeutic for prevention of CI after TBI.This work was supported by NINDS R01 NS111120

Ultrasonic vocalization playback as an affective assay at both neural and behavioral levels: Implications for understanding adversity-induced emotional dysfunction.

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Understanding the effects of early life adversity (ELA) through maternal separation in rats provides a translational window to study behavior and mood disorders in humans with a history of ELA. We are developing and characterizing a translational rat model comparable to the human fearful face task. In rats, ultrasonic vocalizations (USVs) are thought to convey similar affective social information to human facial expressions. Here, we consider how ELA exposure affects responses to aversive (22 kHz) and appetitive (55 kHz) USVs in male and female rats across development. By exposing ELA and control rats to 22 or 55 kHz USVs as a probe for hypervigilance and/or dysfunction in affective processing, we can examine how ELA impacts behavioral responses to emotionally valanced stimuli. Male and female rats were evaluated in an open field test (OFT) at postnatal day (PD) 25 and PD 45 to assess whether responses to playback may be influenced by an interaction between development and ELA history. In a second experiment, male and female rats were exposed to silence, 22 or 55 kHz USVs, or a 38 kHz tone as an ultrasonic control during the OFT. Results from both studies suggest that there are distinct behavioral responses to USV stimulus playback over time in the OFT. Differences in behavior between sexes, developmental ages, and ELA exposure suggest the likelihood of different processing of aversive and appetitive USVs. Examination of cFos in conjunction with GABAergic (parvalbumin) markers of activated cells provide insight into the role of inhibitory neural recruitment during USV playback across regions of the brain central to affective processing, including prefrontal cortex, nucleus accumbens, bed nucleus of the stria terminalis, and basolateral amygdala. This model gives us the opportunity to characterize patterns of activity in the brain that correspond with emotionally valanced social signals and behavioral output. The unique behavioral and neural responses to these stimuli allow us to determine how processing of potential threat or positively valanced social cues may be altered in both typically developing organisms and those with a history of adversity. Funded through NIGMS (P20GM103423).

The Serotonin 2A Receptor Regulates Synaptic Plasticity of Claustrum Cortical Projection Neurons: Implications for Cocaine-Induced Cognitive Deficits

Anderson, Tanner; Ortinski, Pavel
The claustrum (CLA), a thin, subcortical nucleus, is the most densely connected structure in the brain and has been surprisingly understudied in neuroscience research. The CLA has been implicated in attention salience and cognitive flexibility and has the highest density of the serotonin 2A receptor (5HT2AR) in brain. 5HT2ARs are the site of action for psychedelic hallucinogens and 5HT2AR agonists are gaining increasing attention in clinical research based on promising findings for treatment of psychiatric diseases such as PTSD, depression, and substance use disorder. The mechanistic relationship between the CLA, 5HT2AR, and cognitive flexibility relevant to substance use remain largely uninterrogated. We propose that cocaine-induced cognitive flexibility deficits rely on the relationship between 5HT2ARs and glutamatergic synapses in the CLA with implications for long-term plasticity and the likelihood to relapse to cocaine use. We observed the effects of cocaine and the potent 5HT releasing agent, MMAI, on rat cognitive flexibility performance using a set-shifting task. Both cocaine and MMAI had profound negative effects on cognitive flexibility performance. Next, we used whole cell recordings to observe effects of 5HT on CLA neurons that project to the anterior cingulate cortex (ACC). CLA-ACC neurons were recorded in the presence of 5HT and the 5HT2AR antagonist, ketanserin. 5HT caused a drastic inhibitory response. Significant decreases in sEPSC frequency and amplitude were observed in CLA-ACC neurons after application of 5HT. Blockade of the 5HT2AR with Ketanserin eliminated the synaptic effects of 5HT, indicating a regulatory role of the 5HT2AR in claustrocortical signaling. Next, we observed spike-timing dependent plasticity (STDP) in CLA-ACC neurons, revealing anti-hebbian long-term depression (LTD). The hallucinogenic 5HT2AR agonist, DOI, reversed this LTD into long-term potentiation (LTP). These findings provide the first physiological evidence that the large population of CLA-ACC neurons are under inhibitory control from 5HT and the 5HT2ARs and suggest long-term synaptic plasticity which contribute to cognitive flexibility deficits following substance use. These data highlight a novel brain target and possible underlying mechanism of substance use disorder.

Neuron-specific cilia loss differentially alters behavioral responses to cocaine in mice

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Despite advancements in our understanding of the mechanisms that mediate neural responses to commonly abused drugs, we still lack a complete understanding of how such compounds exert their influence on the brain and behavior. In recent years, neuronal primary cilia have garnered much attention for their role in a variety of neurobehavioral contexts including drug responses, thus offering a new landscape to explore. Primary cilia are microtubule-based organelles that project from the surface of nearly all mammalian cells, including neurons. They function as signaling hubs and are enriched with a diverse array of GPCRs, including several known to be associated with motivation and drug-related behaviors; however, our understanding of how cilia regulate neuronal function and behavior is still limited. We previously showed that neuronal cilia loss alters locomotor responses to amphetamine in a cell-type specific manner. The objective of the current study was to investigate the contributions of primary cilia on specific neuronal populations to behavioral responses to cocaine. To test the consequences of cilia loss on cocaine-induced locomotion and reward-related behavior, we selectively ablated cilia from dopaminergic or GAD2-GABAergic neurons in male and female mice. Cilia ablation on either dopaminergic or GAD2-GABAergic neurons failed to significantly alter acute locomotor responses to cocaine at a range of doses (3, 10, & 30mg/kg). With repeated administration, mice lacking cilia on GAD2-GABAergic neurons exhibited enhanced locomotor sensitization to cocaine at 3mg/kg compared to wild-type littermates, whereas mice lacking cilia on dopaminergic neurons exhibited reduced locomotor sensitization to cocaine at 10 & 30mg/kg. To test the rewarding effects of cocaine we used a conditioned place preference test. Preliminary data indicate that mice lacking cilia on GAD2-GABAergic neurons show no difference in cocaine CPP, whereas mice lacking cilia on dopaminergic neurons exhibit reduced CPP compared to wild-type littermates. Combined, our results show that behavioral effects of cilia ablation are cell- and drug type-specific, and that neuronal cilia regulate both the locomotor-inducing and rewarding properties of cocaine.

Prelimbic cortex neural encoding in an Alzheimer's disease rat model during an outcome devaluation task.

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Alzheimer’s disease (AD) is characterized by the accumulation of neuropathological markers and profound memory loss. AD rats (TgF344-AD) expressing mutant amyloid precursor protein and presenilin-1 exhibit age-dependent progressive AD pathology (plaques, tau pathology, oligomeric AÎ² and neuronal loss) and show hypofunction within the prelimbic cortex (PrL) at 6 months. We have shown that PrL neural activity during learning predicts, and is necessary for, ratsâ€™ ability to suppress behavior following outcome devaluation. We investigated if AD rats would show aberrant neural activity and/or behavioral responding to reward predictive cues following outcome devaluation. AD rats (n=6) and wild-type littermate controls (n=6) were presented with two distinct cues as conditioned stimuli (CS+; predicting a sugar or food pellet) and two cues that did not predict a reward (CS-); 10 trials each. After 10 sessions, rats underwent a devaluation procedure to induce a conditioned taste aversion (LiCl, i.p., 0.3 M; 7.5 ml/kg) to one reward. Rats were then tested on the same Pavlovian task (under extinction) to evaluate their ability to avoid the CS+ associated with the devalued outcome. WT rats spent less time in the food cup during the devalued CS+ (13.6%) compared to the non-devalued CS+ (21.0%). AD rats did not differ in the time spent in the food cup during the devalued CS+ compared to the non-devalued CS+ (10.9% vs. 14.3%). PrL electrophysiological recordings revealed distinct neuronal populations that were â€œphasicâ€• to the CS+ [excited, EXC; or inhibited, INH]. In WTs, there was a lower % of PrL neurons that were classified as phasic to the devalued CS+ (26.5% of total) compared to the non-devalued CS+ (44% of total), while, in AD rats, the % of PrL neurons that were phasic were the same to both devalued CS+ (26% of total) and non-devalued CS+ (29% of total). Phasic neurons in AD rats were primarily excited to both the devalued (3% INH, 23% EXC) and non-devalued CS+ (9% INH, 20% EXC), whereas the phasic neurons in WT rats were primarily inhibited to both the devalued (20.5% INH, 6% EXC) and non-devalued CS+ (32% INH, 12% EXC). AD ratsâ€™ aberrant behavioral responding may be a result of atypical mPFC encoding. R00DA042934 (NIA and NIDA)

Enabling Concentration-Response Analyses for Neuropsychopharmacology.

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Drugs exert their behavioral effects via concentration-dependent actions upon neural circuits. However, to date, there has been relatively limited attention to the role pharmacokinetics plays in psychopharmacology because, amongst other factors, the temporal resolution with which we can measure these compounds is orders of magnitude too slow to capture the concentrations associated with altered physiological processes. For instance, procaine and cocaine are psychoactive compounds that have short half-lives and elicit highly dynamic behavioral effects upon intravenous administration making determination of the relation between in-brain concentration and on-going behavior challenging. Thus motivated, we adopted electrochemical aptamer-based sensors (E-AB sensors) to the task of measuring drugs in-situ and in real-time in awake, freely behaving animals. Here, we report EAB sensors that exhibit sufficient sensitivity, appropriate temporal resolution (~12s), and stable drift characteristics to fully resolve pharmacokinetics of procaine and cocaine in the brains of rats.These data combined with standard locomotor measurements enable detailed analyses of the relations between in-brain concentration and behavioral response for individual male and female subjects. In parallel, we employed EAB-supported feedback-control of drug delivery to produce constant in-brain drug concentrations to remove individual differences in PK as well as examine within-session neurobehavioral adaptations caused by drug exposure. In conclusion, we have developed technology capable of determining individual, in-brain pharmacokinetics of psychoactive drugs in behaving animals that can enable concentration-response analyses. Funding Acknowledgement: Supported by NIH grants R01AI145206 and R01DA51100.

Optogenetic manipulation of direct and indirect pathways during interval timing in mice.

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Precisely controlling the timing of movement is a critical human faculty that is impaired in many neuropsychiatric disorders. Timing depends on dopamine activity in the dorsomedial striatum and manipulating striatal dopamine levels causes changes in temporal estimation. However, dopamine has differential effects on direct (dMSN) and indirect (iMSN) pathway spiny projection neurons. Canonically, these distinct pathways are thought to play oppositional roles in movement, and therefore we sought to characterize their roles in timing. We tested timing behavior using a task which requires mice to respond at either a short or a long port based on their estimation of the duration of an interval. We optogenetically stimulated or inhibited dMSNs or iMSNS by delivering pulses of light to dMSN terminals in the substantia nigra pars reticulata or iMSN terminals in the external globus pallidus. We found that inhibition of both pathways led to an increase in the estimation of time. Activation of the direct pathway also led to similar overestimations, but activation of the indirect pathway led to an underestimation of temporal intervals. Our results suggest a heterogenous role for striatal DA in timing, and complexity in dMSN and iMSN response. We will test this hypothesis by recording from neuronal ensembles in downstream targets of each pathway, and through optogenetic manipulations of these structures. Our work may lead to targeted, cell-type specific, and novel pharmacological interventions for disorders of dopamine like Parkinson’s Disease. Funding: 5R01MH116043-04.

Social Defeat Stress is Consolidated as a Fear Memory in a Social Context-Dependent Manner.

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Physical stressors are commonly used to study the neurobiology of fear memory. However, mammals are social animals, and they are frequently exposed to social stressors, for example bullying. The aim of this study was to investigate the effects of aversive social experiences on memory consolidation and social behavior. We evaluated whether the experience of social stress is consolidated as a classic fear memory and whether it has any impact on social interaction. Adult male Sprague Dawley rats were subjected to the chronic social defeat stress paradigm while the other group was left undisturbed (control group). Three parameters were assessed: 1) locomotor activity using the open field test, 2) freezing behavior as a measure of conditioned fear in the context of social defeat, and 3) social interaction. Animals that were subjected to chronic social defeat stress had an increase of freezing time and low freezing latency compared to the control group. Time spent in social interaction decreased in the stressed rats compared to controls, while time spent in freezing behavior increased in the social interaction task. Our results suggest that the experience of social defeat is consolidated as a fear memory that generalizes to social behavior. Social defeat stress attenuated social interaction and activated fear responses when the rats interacting with an unfamiliar animal. The social defeat paradigm offers the opportunity to study the neurobiology of social aversive experiences on memory and social behavior. This study was funded by FONDECYT (Grant Number 1141276) and Anillo de Ciencia y TecnologÃa, Programa PIA of CONICYT (Grant Number ACT1403) to Alexies Dagnino-Subiabre. The authors report no conflict of interests.

Therapeutic potential of miconazole in a mouse model of chemotherapy-induced cognitive impairment.

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The quality of life in cancer survivors is often affected by the long-term cognitive consequences of chemotherapy, which is known as chemotherapy-induced cognitive impairment (CICI). CICI include areas of cognitive functioning, such as executive functions, information-processing speed, attention, memory, and learning. Furthermore, CICI has been related to leukoencephalopathy (white matter damage). In this preclinical study, we examine the long-term (adult) consequences of triple systemic injections of the chemotherapeutic methotrexate (MTX) in juvenile mice, which mimics the MTX exposure in children treated for acute lymphoblastic leukemia. We also investigate the putatively attenuating effects of miconazole, an antifungal agent currently studied for its remyelination properties. Female juvenile C57BL/6 mice are injected with MTX (or saline) on postnatal days 21, 28, and 35. Afterwards, half the animals receive pharmacological intervention with miconazole. Mice receive one daily injection of miconazole (or saline) from postnatal day 36 through 42. During adulthood, subjects are tested on a broad behavioral battery that assesses aspects of cognition, social behavior and emotional reactivity. Lastly, using immunohistochemical analyses, we inspect myelin basic protein expression in the brain, a biomarker of white matter integrity. We expect miconazole to alleviate myelin damage that underlies the behavioral symptoms associated with MTX exposure. An intervention with miconazole is of translational value. It may function as a remyelinating drug with no effect on the immune system, making it a potentially safe and effective adjuvant in leukemia therapy. This work was supported by the Olivia Hendrickx Research Fund, Belgium.

Considering a role for dopamine in dieting using a mouse model.

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Our modern food environment is full of highly palatable, calorie-dense foods that are easy to overeat - consume excess calories. In this environment, the number of individuals that overeat to the point of developing obesity and associated health consequences has skyrocketed. Despite the growing awareness of the detrimental effects of overeating, individuals with and without obesity find it very difficult to diet, or to reduce overeating by switching to less- palatable, lower calorie food options. To explore the behavioral and neural basis of dieting difficulties, we developed a short-term mouse model of overeating and dieting. In our model, mice are given ad libitum access to high-fat diet (60% fat) for 3 days before being switched back to chow. They robustly overeat during high-fat diet access and then dramatically reduce their chow intake on the switch day (diet day) relative to their intake before high-fat diet. Further, the chow undereating effect is not exclusive to the lard-based high-fat diet nor to the lack of food choice during high-fat diet access. Many have hypothesized that increased preference/craving for palatable foods plays a critical role in derailing diets, and we believe the undereating effect reflects another important driver of dieting difficulty- reduced preference/motivation for less-palatable alternatives. Thus, given that dopamine signaling in the nucleus accumbens is implicated in encoding reward value and invigorating behavior, and that altered dopamine signaling has been linked to enhanced cravings for and overconsumption of palatable foods, we are currently using fiber photometry to assess whether dopamine release in the nucleus accumbens reflects changes in motivation to consume chow across the time course of this short-term model. This work was supported by NIDA Supplement 3R01DA049924-03S1 to WCF.

Distinct roles for prefrontal dopamine D1 and D2 neurons in social hierarchy.

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Neuronal activity in the prefrontal cortex (PFC) controls dominance hierarchies in groups of animals. Dopamine (DA) strongly modulates PFC activity mainly through D1 receptors (D1Rs) and D2 receptors (D2Rs). Still, it is unclear how these two subpopulations of DA receptor-expressing neurons in the PFC regulate social dominance hierarchy. Here, we demonstrate distinct roles for prefrontal D1R- and D2R-expressing neurons in establishing social hierarchy, with D1R+ neurons determining dominance whereas D2R+ neurons for the subordinate. Ex vivo whole-cell recordings revealed that the dominant status of male mice correlates with rectifying AMPA (Î±-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor transmission and stronger excitatory synaptic strength onto D1R+ neurons in PFC pyramidal neurons. In contrast, the submissive status is associated with higher neuronal excitability in D2R+ neurons. Moreover, simultaneous manipulations of synaptic efficacy of D1R+ neurons in dominant male mice and neuronal excitability of D2R+ neurons of their male subordinates switch their dominant-subordinate relationship. These results reveal that prefrontal D1R+ and D2R+ neurons have distinct but synergistic functions in the dominance hierarchy, and DA-mediated regulation of synaptic strengths acts as a powerful behavioral determinant of intermale social rank. This study was supported by NIH R21MH110678, the NIH R01MH085666, NARSAD Independent Award 2015, and Pennsylvania Commonwealth 4100072545 (CURE 2016) to W. J. Gao.

Temporally-specific inhibition of ventral tegmental area dopamine neurons during decision making under risk of punishment.

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Decision making is a complex behavior that necessitates numerous brain regions working in concert to obtain a desired outcome. At the root of this behavior lies dopamine signaling arising from the ventral tegmental area (VTA). The VTA plays a fundamental role in biasing decision-making processes, and dysfunction in this system accompanies maladaptive decision making in conditions such as substance use disorder. To further elucidate the functional role of the VTA in decision making, male and female tyrosine hydroxylase-cre transgenic rats were utilized to selectively drive halorhodopsin expression localized to dopaminergic neurons of the VTA. Rats were then trained on a risky decision-making task (RDT) in which they made discrete choices between two levers: a small reward lever that dispensed one food pellet and a large reward lever that dispensed two food pellets accompanied by variable risks of mild footshock (0%, 25%, 75%). Rats were implanted with optic fibers targeting the VTA, through which 560 nm laser light was delivered to selectively inhibit VTA dopaminergic neurons during discrete timepoints of the decision-making process (during deliberation prior to lever selection, during receipt of the small reward, during receipt of the large reward with or without punishment, or during the intertrial interval). Preliminary findings show that inhibition of VTA dopamine neurons during receipt of the large reward in the absence of punishment causes rats to become more likely to choose the small safe reward on subsequent trials. This shift toward risk-averse behavior is supported by our current understanding of reward prediction error signaling, with optogenetic inhibition of dopamine neuron activity potentially mimicking a reduction in tonic firing as found with negative prediction errors (i.e., a signal that the outcome of a choice was worse than expected). This project is supported by R01DA036534, R01AG060778, K99DA041493, 5T32AG061892-04 and the McKnight Brain Research Foundation and McKnight Brain Institute Funds.

Intraperitoneal IGF1 treatment improves ischemic stroke-induced affective and cognitive behaviors in acyclic middle-aged female rats

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Our previous studies have modeled the post-menopausal female population, which are at a higher risk for and display worse outcome post stroke, using acyclic middle-aged female rats. This group has lower circulating and parenchymal levels of the peptide hormone IGF-1. ICV administration of IGF-1 to this group decreases infarct volume, improves blood brain barrier permeability and reduces cytokine levels in the ischemic hemisphere. Despite this neuroprotection, icv IGF1 treatment did not improve cognitive decline and depressive behaviors in the chronic phase of stroke. In view of the evidence that stroke induces gut dysbiosis, and that gut dysfunction is implicated in depressive and cognitive behaviors, we hypothesize that, unlike icv IGF-1 treatment, which is restricted to the brain, systemic (i.p.) IGF1 treatment would repair the gut, attenuate peripheral cytokine levels and improve long-term behavior outcomes. Acylic middle-aged Sprague Dawley female rats were subjected to MCAo or sham operation. Animals received i.p. IGF1 injections 4h and 24h post MCAo, or icv infusions, while controls received vehicle. Sensory motor tests, blood and gut samples were acquired pre and post MCAo. Animals were terminated either in the acute phase (2d) or chronic phase (30d). The latter group was also subject to tests of cognition and depressive-like behavior. In contrast to icv treatment, i.p.-IGF-1 did not reduce infarct volume or acute sensory motor impairment but significantly attenuated circulating levels of TNFa and IL17 and post stroke gut dysmorphology, by preserving villus:crypt ratio. In addition, i.p. IGF1 treatment attenuated the cognitive deficits post stroke as seen in the Barnes Maze and NORT assays as well as depressive outcomes in the burrowing assay. Since long term disability after stroke is correlated with elevated levels of peripheral cytokines, our data suggest that systemic IGF1 may be a better therapeutic option for long term cognitive and depressive behaviors after stroke. Acknowledgements: Supported by NS074895, AG042189 and TAMU Presidential Impact Fellow Award to FS

TIME AND DOSE-DEPENDENT EFFECTS OF CORTICOSTERONE INHIBITION ON LEARNING AND CONSOLIDATION OF THE CUED WATER MAZE TASK

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Animals learn, store, and retrieve information about experiences that are encoded by different systems in the brain. The dorsal striatum (DS) is involved in processing stimulus-stimulus and stimulus-response associations. Stress can modulate these types of learning, as it is associated with the release of hormones such as glucocorticoids (corticosterone in rodents). One stress-related task that allows studying stimulus-response behavior in a stressful context is the cued water maze (CWM), which depends on the activation of DS. The aim of this work was to study whether the inhibition of corticosterone (CORT) synthesis with metyrapone (MET) impairs the acquisition and consolidation of the CWM task. To this end, male Wistar rats received vehicle (VEH) or MET (7.5, 50, or 75 mg/kg) 90 min before training. Other groups received MET (75 mg/km) or VEH 60 or 30 min before training. The training consisted of one session of eight trials and 48 h later the rats were tested on four trials and a probe test (one trial without a platform). MET (50 and 75 mg/kg) 90 min before training produced slower learning and impaired memory, while the dose of 7.5 mg impaired memory but did not interfere with the acquisition. MET 75 (mg/kg) given 60 min before training caused memory impairment but did not affect acquisition; the same dose of MET given 30 min before training did not affect acquisition and retention. In the probe test, all the MET groups showed impairment in stimulus-response memory but spatial memory was spared. We conclude that the timing at which MET was administered and its effects are related to the time of the maximum inhibitory effect (between 1 and 1.5 h after administration). CORT can modulate the acquisition and consolidation of stimulus-response memory. The inhibition of CORT impairs stimulus-response behavior and promotes the use of spatial behavior. We thank N. Serafín, A.C. Medina, M. García, A. Castilla, M.A. Carbajo, B. Osorio, R. Martínez, M.E. Rosas, and N. Aranda for their excellent technical assistance. Supported by CONACYT (Scholarship 521004127) and PAPITT-DGAPA (IN209822).

Sex-dependent activity in anterior cingulate cortex modulates offspring interactions.

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How sexually divergent behaviors arise from differences in the underlying neural networks for social behavior remains elusive. Interestingly, mice show pronounced sex differences in pup directed behaviors. When the pups are away from the nest, the mother retrieves them to keep them warm. This behavior is not consistently observed in males, and differs in several respects. Our data suggest that paternal behavior is subject to additional contextual regulation compared to maternal behavior. To compare the networks that underlie parenting in males and females, we used c-fos as a marker for neuronal activation after pup interactions, and an automated pipeline to map whole-brain activity at cellular resolution using light-sheet microscopy. We identified brain regions that responded to pup interactions including the anterior cingulate area (ACA). We chose to focus on ACA because it has been implicated in sensitivity to social distress and it is interconnected with the locus coeruleus (LC), an important regulator of maternal behavior. We used fiber photometry to observe activity in ACA and LC during interactions with pups. Briefly, the technique involves injecting an adeno-associated virus (AAV) driving expression of the activity reporter GCaMP and implanting an optical fiber to deliver excitation light and carry the activity-dependent fluorescent emitted light to a photodetector. We found that excitatory neurons in ACA are differentially activated in males and females during pup retrieval behavior and that inhibitory neurons show reciprocal activation. We also observed that pup retrieval behavior evokes strong sex-dependent neuronal responses in LC. Moreover, we confirmed that ACA receives robust inputs from LC, and using a noradrenaline sensor, we observe that pup retrieval behavior evokes noradrenaline release in ACA. Finally, we showed that chemogenetic inactivation of excitatory neurons in ACA disrupts pup retrieval behavior and decreases parental motivation. Based on these findings, we hypothesize that ACA signals distress from the pups and guides decision making in parenting behavior. Moreover, sexually divergent activation of this circuit may contribute to behavioral differences between males and females. Support: R01MH119250

Social and environmental positive stimuli can increase NPY expression in Long-Evans rats exposed to unpredictable chronic stress.

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Positive interactions with the social and physical environment can promote resiliency by shaping the neural circuitry responsible for mitigating the negative effects of chronic unpredictable stress. The main aim of this study was to identify the influence of social play and environmental enrichment on neural resiliency in Long-Evans rats. Neuropeptide-Y (NPY) immunoreactivity was measured in several key areas related to coping and stress: the amygdala, hippocampus, and periventricular nucleus (PVN) of the hypothalamus. Additionally, corticosterone (CORT), dehydroepiandrosterone (DHEA), and testosterone (T) metabolites were collected to measure physiological plasticity in the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes. Male rats (n=60) were randomly assigned to either standard or enriched housing, and a group of 20 rats were randomly selected to play with an unfamiliar conspecific for five minutes over 21 days. Rats assigned to enriched housing were placed in standard sized cages containing natural objects, such as a hideaway, rocks, and climbing sticks. These objects were meant to stimulate the cognitive and emotional response of the rats, as well as provide opportunities for physical interaction such as hiding or climbing on the objects. All rats were exposed to a combination of several unpredictable chronic stressors three times a week for the duration of the experiment. Animal play behavior was videorecorded and analyzed to determine the frequency and duration of social interactions. Preliminary results indicate there was a relationship between playing, enrichment, and neurophysiological functions. Specifically, playing improved coping regulation by significantly increasing NPY expression in the PVN. Both the HPA and HPG axes were also influenced by social and environmental stimuli: animals who were exposed to play and natural enrichment had a significantly higher DHEA/CORT ratio and lower T levels. Current events have increased exposure to uncontrollable stressors and social isolation for large portions of the human population. These results of this study indicate that we could regain control in these difficult circumstances by increasing our social support and positive environmental interactions.

The role of the nucleus accumbens shell in alcohol use despite negative consequences

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Alcohol use is widespread across most societies. While most people can control their alcohol use, a vulnerable sub-population develops alcohol use disorder (AUD), characterized by continued alcohol use despite negative consequences. We used a rat model of alcohol use despite negative consequences, to identify neurobiological activity that may underlie addiction-like behavioral vulnerability. It was previously shown that this approach reliably identifies two sub-populations. One group substantially decreases alcohol use in the face of punishment (punishment-sensitive, controlled use) and another group continues alcohol use despite negative consequences (punishment-resistant, addiction-like behavior). In this study, we aim to identify the role of the nucleus accumbens shell (NAcSh) in alcohol use despite negative consequences. We trained Long-Evans outbred rats (n=92, m/f) to self-administer alcohol, and then introduced punishment with response-contingent foot-shock. Interestingly, we found that more female rats developed punishment-resistant alcohol use compared to male rats. In one group of rats (n=24) we used immunohistochemical detection of c-Fos to identify brain activity associated with punishment-resistant alcohol use. We found that lower c-Fos expression in NAcSh was associated with punishment-resistant alcohol use, compared to punishment-sensitive use, and rats tested without punishment. To test for a causal role of NAcSh activity in punishment-resistant alcohol use, in another group of rats (n=68) we used chemogenetic inhibition (hM4Di) of NAcSh throughout different phases of the experiment. We found that chemogenetic NAcSh inhibition does not affect unpunished alcohol self-administration. In punished sessions, however, NAcSh inhibition showed a small but significant increase in punished alcohol seeking only in punishment-resistant rats at higher shock intensities. These results imply that NAcSh may be involved in alcohol use despite negative consequences in vulnerable individuals. Understanding the contribution of NAcSh, and associated neural circuits, in alcohol use despite negative consequences will provide us with a greater understanding of the neurobiological underpinnings of AUD.

Characterizing the role of the posterior intralaminar complex of the thalamus in social behavior in mice.

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The neuropeptide oxytocin (OXT) is produced in the hypothalamus of the brain and is implicated in the expression of social behaviors. Within the hypothalamus, glutamate has been shown to drive synchronized OXT cell firing and burst release of OXT. However, the origin of glutamatergic inputs to the hypothalamus and their role in social behaviors has been understudied. Using viral retrograde tracing and immunohistochemistry in mice, we first identified several key brain regions which send glutamatergic inputs to the paraventricular nucleus of the hypothalamus (PVH) and are known to be involved in the processing of sensory stimuli and social behaviors. Of primary interest is the posterior intralaminar (PIL) complex of the thalamus, which, using a modified rabies virus system, we show inputs directly onto OXT neurons in the PVH. To investigate whether the PIL is involved in social interaction, we exposed adult male and female mice to either a novel, same-sex juvenile social stimulus or a novel object stimulus for 1 hour of free interaction. After, brains were collected and analyzed for immunohistochemical staining of the immediate early gene c-fos. We observed significantly more c-fos+ cells in the PIL of mice exposed to social stimuli compared to those exposed to object stimuli, indicating that the PIL is selectively activated during social interaction. To confirm these results in real-time, we used fiber photometry to record neural activity of glutamatergic neurons in the PIL during social and object interaction in mice. Our preliminary recording data demonstrates that the neural activity of glutamatergic PIL neurons is increased when mice are engaged in social interaction and decreased when they move away from the social stimulus. We expect our findings to identify novel roles for glutamate-OXT circuits, which may further contribute to our understanding of neural mechanisms involved in social behaviors. This work was supported by the Beatrice and Samuel A. Seaver Foundation Fellowship from the Seaver Autism Center for Research and Treatment at Mount Sinai and the National Institute of Mental Health of the National Institutes of Health under Award Number F31MH129025.

Dopaminergic plasticity underlying bonding and loss in monogamous prairie voles

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While healthy social relationships positively contribute to our health and wellbeing, their loss is profoundly detrimental. In monogamous prairie voles, dopamine (DA) release in the nucleus accumbens (NAc) plays a critical role in the formation and maintenance of pair bonds. Yet despite the central role for this neuromodulator in reward, aggression, and aversion, we lack an understanding of how plasticity within dopaminergic systems contribute to bonding or the response partner loss. To test the hypothesis that bonding and loss result in changes in DA release dynamics, my work leverages GRABDA, a fluorescent DA sensor detectable via fiber photometry, to measure DA release in the NAc of behaving voles. We employed a longitudinal approach to determine if bonding changes DA release dynamics. In a first experiment, we optogenetically activated the ventral tegmental area while measuring DA in the NAc, asking whether the same optical stimulation resulted in social experience-dependent differences in DA release. We found that pairing with an opposite-sex partner led to decreased optically evoked DA release during early but not later timepoints. In addition, partner separation, a model of bond loss, decreased evoked DA release relative to that observed in a mature bond. Compellingly, we also found that voles with the greatest change in DA release 30 days after partner separation spent the most time with their partner upon reunion. This suggests that plasticity in DA release dynamics may contribute to individual differences in response to partner loss. In a second experiment, we used a social operant choice task to detect partner versus non-partner differences in natural DA release. Preliminary results show that DA levels are lower prior to lever pressing for a non-partner compared to a partner. Additionally, when crossing into the partnerâ€™s chamber, DA release is sustained at higher levels compared to crossing into a non-partnerâ€™s chamber. These preliminary results point to higher levers of DA release during partner related tasks, which could serve to maintain the bond over time. Our work provides insights into the dopaminergic dynamics that contribute to social attachment and adaptation to loss.Funded by NIH R36MH129127 and DP2MH119427.

Characterizing the role of the posterior intralaminar complex of the thalamus in social behavior in mice

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Deficit in attention, increased impulsivity and cognitive impairment are behavioural endophenotypes of some neuropsychiatric disorders including Attention-deficit/hyperactivity disorder (ADHD). Currently available medication such as methylphenidate and amphetamine targeting dopaminergic and noradrenergic transmitter systems to treat these behavioural endophenotypes has the side effect of becoming addictive. Therefore, it is essential to investigate an alternative safer therapeutic cure. Orexin neuropeptides are synthesized in the lateral posterior hypothalamus and perifornical area. On its discovery in the year 1998, orexin was simultaneously found to play a role in feeding behavior and in the maintenance of the sleep/wake cycle. Given the brainwide projections of orexin neurons, later research indicated roles of orexin in motivation, cognition, fear and anxiety. It has been shown that children with ADHD have low levels of orexin neuropeptide in their blood serum. In our study, we investigated the role of orexin neuropeptide in attention and impulsivity using the 5-choice serial reaction time task in male and female orexin-deficient mice. Since, orexin neuropeptide levels alter during light/dark cycle, we performed the task during both the cycles in an automated touch screen chamber. Interestingly, we found that orexin deficiency decreased baseline impulsivity during the light phase in male but not in female homozygous orexin-deficient mice indicated by reduced premature responses. We further investigated the role of orexin in psychostimulant (Dizocilpine) induced cognitive impairment in a touchscreen visual discrimination task. Our preliminary result shows sex-difference in dizocilpine mediated cognitive impairment. Our results indicate sex-dependent role of orexin in behavioural endophenotypes of neuropsychiatric disorder. (This study is funded by Deutsche Forschungs Gemeinschaft (FE 483/10-1), Germany)

Lipopolysaccharide-induced neuroinflammation in the posterior dorsomedial striatum facilitates goal-directed action.

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Neuroinflammation has been identified in the striatum of individuals with compulsive disorders. These individuals also display deficits in goal-directed action. Nevertheless, a direct, causal link between striatal neuroinflammation and impaired goal-directed action has yet to be established. We therefore used rats to investigate such a link. In Experiment 1, rats received micro-injections in the posterior dorsomedial striatum (pDMS) of either saline or the endotoxin lipopolysaccharide (LPS) (5mg/ml) to induce neuroinflammation. We then examined goal-directed decision-making performance using Pavlovian-instrumental transfer and outcome devaluation. In the Pavlovian phase, rats were trained to associate two unique auditory cues with pellets and sucrose (counterbalanced). In the instrumental phase, the same rats were trained to press left and right levers for pellet and sucrose outcomes respectively (counterbalanced). When animals were overfed and control effects were small, transfer and devaluation were comparatively enhanced in group LPS. That is, during transfer testing when presented with the auditory cues, group LPS selectively responded on the lever associated with the same outcome (Same>Different) whereas group Sham did not. During devaluation testing, when fed to satiety on one outcome and subsequently given a choice between levers, although both groups responded more on the lever that had earned the valued relative to the devalued outcome, this difference was larger in group LPS. Experiment 2 tested whether pDMS neuroinflammation increases motivation generally, or goal-directed action specifically. Here, we trained sham and LPS pDMS animals to press a single lever for sucrose on an interval schedule over 15 sessions. When tested for progressive ratio performance, animals in group LPS reached consistently higher breakpoints than group Sham. Upon devaluation testing, group Sham demonstrated evidence of habits (Valued=Devalued) and group LPS demonstrated intact goal-directed actions (Valued>Devalued). Together, these results suggest that LPS-induced neuroinflammation in pDMS increases both motivation and goal-directed action, possibly akin to a person who compulsively seeks rewards under low motivation conditions. This work was supported by Australian Research Council.

Sex-specific variation of catecholamine regulatory proteins may underlie increased risky choice preference following repetitive mild traumatic brain injury.

Mild traumatic brain injury (mTBI) accounts for 75% of reported head traumas. Injury-induced disruption of cognitive processes can lead to increased risk-taking behavior. The medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), and anterior cingulate (ACC) of the PFC play prominent roles in risk/reward decision making. Currently, little is known regarding the effects of repetitive (rmTBI) or whether these outcomes differ in men vs women. Here we examined how rmTBI affects risk/reward behavior in rodents using a probabilistic discounting task (PDT) that mimics risky gambling behavior in humans. Rats are required to choose between a small/certain reward delivered with 100% certainty or a large/risky reward delivered with decreasing probabilities over a session. Rats were trained in the PDT, exposed to a single or a series of 3 closed head control cortical impact (CH-CCI) injuries within 1 week, and then returned for 4 weeks of testing. RmTBI increased risky choice in female, but not male rats during the first 2 weeks post injury. Choice behavior normalized in weeks 3 and 4 post injury, indicating that these effects are transient. Previous reports have shown that catecholamine transmitter levels are immediately increased, but then persistently decreased within the PFC following TBI, suggesting imbalances within the PFC may underlie TBI-induced behavioral outcomes. To further investigate our observations and potential mechanisms of catecholamine imbalance within the PFC, Western blotting was used to measure levels of the packaging enzyme, VMAT2, and degradation enzymes, COMT and MAO, in PFC sub-regions 1 week after rmTBI. VMAT2 and COMT were both reduced in the OFC of rmTBI males and females, while MAO-A was only reduced in the OFC of rmTBI females. Decreased VMAT2 indicates less capacity for packaging and release, while decreased COMT and MAO-A may reflect decreased need for degradation. The sex-specific decrease of MAO-A in the OFC of rmTBI females may serve as a novel variable to further elucidate differential rmTBI-induced mechanisms of increased risky choice preference. As such, combining the CH-CCI model of rmTBI, PDT, and Western blotting creates an innovative model for studying the effects of TBI on male vs female subjects and the neural mechanisms underlying behavioral changes. Funding sources: New Jersey Commission on Brain Injury Research CBIR20PIL004 and CBIR19IRG025, and Osteopathic Heritage Foundation for Primary Care Research.
Effects of reproductive experience on cost-benefit decision making in females

Effects of reproductive experience on cost-benefit decision making in females

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The variable of reproductive experience is largely neglected in behavioral neuroscience research, as almost all studies use reproductively naïve animals. Majority of women undergo reproductive experience at some point in their lives, and pregnancy and childbirth have been reported to be associated with alterations in risks of several psychiatric disorders. Research in rodents shows that maternal experience affects spatial learning and other aspects of hippocampal function. Yet, there has been little investigation of how reproductive experience affects cost-benefit decision making, despite the relevance of this aspect of cognition for psychiatric disorders. To begin to address these issues, we used female Long-Evans rats to perform impulsive and risky decision making tasks in standard operant chambers. Rats in the parous group were mated, gave birth, and nursed for 21 days until pup weaning, and rats in the nulliparous group were unmated. One week after pups were weaned rats began behavioral testing. Rats were initially tested in a delay discounting task, in which they made discrete trial choices between a small immediate food reward and a large food reward delivered after a variable delay period, where an interaction between group and delay duration was observed. Next, in a risky decision-making task, rats made discrete trial choices between a small, safe food reward and a large food reward accompanied by variable probabilities of mild footshock punishment. There was an interaction between group and shock probability on this task, however, parous rats chose the large reward more frequently than nulliparous, suggestive of greater risk taking in this group. To investigate effects of reproductive experience on food motivation, rats were tested on a progressive ratio schedule of reinforcement. Our results revealed no differences between groups, indicating that nulliparous and parous rats were comparably motivated to obtain the food reward. Together, these results show distinct effects of reproductive experience on different forms of cost-benefit decision making in females, and highlight reproductive status as a variable that may influence aspects of cognition relevant for psychiatric disorders.

Chronic corticosterone administration alters synaptic mitochondrial function within the hippocampus of C57Bl/6 mice in a sex-specific manner.

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Increases in circulating corticosterone (CORT) levels are a result of the chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis. In vivo, this can be triggered by chronic stress and trauma, causing a host of downstream behavioral, molecular, and metabolic changes in a sex-specific manner. Here, we aim to determine if an increase in circulating CORT alone gives rise to the sex-specific changes in behavior and mitochondrial respiration in hippocampal (HPC) synaptosomes of male and female mice. Adult male (n = 15) and female (n = 17) mice were given 35ug/mL CORT via their drinking water, or drinking water with vehicle for 21 consecutive days. Mice were assessed in the open field for anxiety-like behavior and the Y-maze for working memory. Functional synaptosomes from the right HPC were isolated and analyzed for mitochondrial activity. HPC synaptosomes were assessed for relative amounts of mitochondria and presynaptic terminal presence using western blotting. Chronic administration of CORT caused a decrease in the overall oxygen consumption rate (OCR) of synaptic mitochondria (SynMt) collected from both males and females. The changes in OCR of SynMt from CORT-treated males was coupled to decreased basal respiration, max respiration, and proton leak when compared to vehicle treated males. Metabolic shifts due to chronic CORT were also evident peripherally as shown by increased body weight compared to vehicle treated controls. Chronic CORT also disrupted health metrics in males such that piloerection was increased in CORT-treated males. Although volume of CORT-containing water was similar between males and females, circulating plasma and fecal CORT were only elevated in CORT-exposed males. Behavioral effects of CORT treatment were evident in the Y-maze such that CORT caused a decrease in max alternations and direct revisits in both sexes treated with CORT. These data demonstrate that although effects of chronic CORT administration are sex-specific for peripheral metrics, the effects on SynMt are similar for both sexes. The reduction in OCR of SynMt following chronic CORT exposure suggests a mechanism by which chronic stress may influence synaptic function.

Adolescent-onset ethanol drinking increases COX-2 and PGE2, and EtOH relapse in adult female rats: antagonism by COX-2 and EP1 receptor inhibitors.

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Adolescent alcohol abuse is a global problem that initiates lifelong alcohol dependence, though the mechanism that mediates this process is unknown. Female adolescents are particularly vulnerable to both early onset alcohol abuse and its long-term negative consequences. Previous studies indicate that adolescent alcohol use increases alcohol use in adulthood and increases pro-inflammatory mediators cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) in the brain, though their roles in relapse to alcohol drinking were not determined. This study uses adolescent voluntary alcohol drinking in female adolescent Sprague Dawley rats to model human alcohol intake and determine long-term changes in COX-2 and PGE2 produced by adolescent drinking. After adolescent alcohol drinking and four weeks of abstinence, rats demonstrated a 32Â±10.3% increase in alcohol intake during relapse and a 71.4Â±24.3% increase in COX-2 in the striatum compared to water drinking controls. COX-2 inhibition with nimesulide during abstinence attenuated alcohol relapse compared to saline-treated controls and returned relapse drinking to the level of alcohol-naÃ¯ve rats. Adolescent alcohol produced a 150.5Â±30.9% increase in PGE2 in the striatum after abstinence that was attenuated by nimesulide treatment to the levels of alcohol naÃ¯ve rats treated with saline. PGE2 activates the PGE2 receptor-1 (EP1 receptor) in the striatum to produce behavioral changes. Therefore, EP1 receptor was antagonized using SC-51089 30 minutes prior to alcohol relapse testing and this antagonism also attenuated alcohol relapse to levels comparable with alcohol naÃ¯ve rats. Based on these findings, a model mechanism of EtOH relapse can be constructed in which adolescent EtOH increases COX-2 in the striatum after abstinence, and elevated COX-2 mediates increased EtOH relapse in adulthood through the PGE2-EP1 receptor interactions. These experiments fill a critical gap in the literature by examining long-term alcohol dependence in females with a history of adolescent alcohol use. Furthermore, this work is the first to identify striatal COX-2 and PGE2 as putative targets for the treatment of relapse to alcohol drinking by adolescent females.Funding Information: NIH, Grant Number DA042737

The effects of Effort-Based Reward training and chemogenetic activation of the lateral habenula on behavioral and neuroendocrine responses in stressful contexts.

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The present study assessed the efficacy of Effort-Based Reward (EBR) training, a behavioral therapy that increases emotional resilience by strengthening associations between physical effort and rewards, on stress responsivity. Of specific interest was the lateral habenula (LHb) due to its role in processing threatening stimuli. Accordingly, the LHb of 30 female Long-Evans rats, assigned to either an EBR contingent-trained group or a control noncontingent-trained group (CON) was bilaterally expressed with hM3Dq (DREADD) or mCherry vehicle (mC). After 4 weeks of training, the LHb was chemoactivated using a synthetic DREADD ligand and animals were tested in two tasks [Novelty Suppressed Feeding Task (NSFT) & Forced Swim Task (FST); with DREADD activation occurring only on the second swim]. In the NSFT that was conducted in an open field with a hiding structure to assess avoidance and approach tendencies, a significant main effect of viral type (p=.004) indicated that DREADD animals entered the area behind the structure at a higher frequency than the mC animals. In the FST, a significant interaction (p=.038) indicated that the EBR animals exhibited decreased float durations from the first to the second swim, an effect not observed in CON animals. Focusing on endocrine responses, a significant interaction (p=.006) indicated that the EBR animals had similar fecal corticosterone metabolite levels at baseline and post-stress measures, whereas CON rats experienced elevated levels at the post-stress sample. A cytokine analysis revealed that DREADD animals exhibited higher pro-inflammatory (IL-1; p=.042) and lower anti-inflammatory (IL-10; p=.024) serum cytokine levels in comparison to mC rats. Thus, the results further corroborate the role of LHb activation in behavioral & immunological threat appraisal and emphasize the context-dependent effects of EBR training on emotional resilience. Further research is necessary to clarify the effects of EBR training on LHb modulation to establish its value as a preclinical model for behavioral therapeutic interventions for psychiatric illness. R15MH117628-01A1.

Aromatase inhibition in the basolateral amygdala impairs heroin extinction memory retention in male and female rodents.

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Misprescription of opioids has led to an opioid use disorder (OUD) epidemic. OUD is characterized by the ability of environmental cues associated with drug use to motivate drug seeking. These cues are extinction-resistant, maintaining their power to drive drug seeking even after numerous presentations of the cue without the reinforcer. Females, among other differences, are more sensitive to drug-associated cues. Yet, exclusion of female subjects from many foundational studies on reward processing have hindered our ability to understand these disparities. We hypothesize that central estradiol (E2) plays a role in sex differences in OUD. In this study, we used fadrozole, an aromatase inhibitor blocking local E2 synthesis, to characterize the role of central E2 in heroin cue extinction memory retention (EMR). Male and female rats self-administered heroin for 6h/d for 8d, where a light/tone cue was co-presented with each infusion. This was followed by 1d of cued extinction (6h; light/tone but no heroin). Just prior to this session, fadrozole was infused into the basolateral amygdala (BLA) through cannulas. The next day, subjects were given a cued EMR test under the same conditions (1h). Females took more heroin than males (mg/kg), despite having similar operant responding, and had higher active nose pokes during the first hour of cued extinction relative to males. All subjects treated with fadrozole in the BLA prior to cued extinction had impaired EMR on test, evidenced by increased active nose pokes relative to vehicle controls (higher drug seeking = poor EMR). Upon examination of the brains, we expect that fadrozole impaired BLA neuronal plasticity on multiple measures and that there is sex differential expression of estrogen receptor (ER) subtypes throughout the BLA. This study is the first to examine a behavioral role for centrally produced E2 in the BLA. Future studies will examine contributions of the different ER subtypes to this behavior and synaptic plasticity, focusing on sex specific mechanisms. A better understanding of sex specific E2 signaling will promote further research on sex differences, allowing us to better address disparities in disorders like OUD. Funding: NIDA P50-DA016511/U54-DA016511, NCATS TL1-TR001451/UL1-TR001450, IBNS

Short-chain fatty acid metabolites modulate cocaine-seeking behaviors.

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Cocaine use disorder represents a public health crisis, yet there are no FDA-approved medications for its treatment. Recent research has detailed the important connections between the brain and the resident population of bacteria in the gut, the gut microbiome. Literature implicates short-chain fatty acids (SCFA), metabolites which are derived from the bacterial digestion of dietary fiber, in mediating behavioral effects in models of neuropsychiatric disease. Our group has demonstrated that depletion of the gut microbiome results in enhanced reward in a mouse cocaine place preference (CPP) model, and repletion of SCFA reverses this effect. Although CPP studies are informative, they do not model relapse to drug-seeking after extended abstinence, which represents a challenge in treating patients. Thus, we examined the effects of microbiome manipulations in a relapse-relevant model. Male Sprague-Dawley rats received untreated home cage drinking water or antibiotics to deplete the gut microbiome and its metabolites. To examine the specific contributions of SCFA, the three primary SCFA (butyrate, acetate, propionate) were replenished to normal physiological concentrations via addition to the drinking water. Rats were trained to self-administer cocaine and subjected to dose-response testing to evaluate motivation to self-administer cocaine at a range of doses or 21 days of abstinence followed by a cue-induced cocaine-seeking task to model relapse behavior. Microbiome depletion did not affect cocaine acquisition on a low effort FR1 schedule. However, when rats who were already stably self-administering cocaine underwent a dose-response task, microbiome-depleted rats exhibited significantly enhanced motivation for low dose cocaine. Similarly, microbiome depletion increased cue-induced cocaine-seeking following prolonged abstinence in a relapse model. Repletion of bacterially-derived SCFA metabolites reversed the behavioral changes associated with microbiome depletion. These findings suggest that gut bacterial metabolites are key regulators of drug-seeking behaviors, positioning the microbiome as an innovative translational research target. Funding was provided to KM (NS124187 and NS117356) and DK (DA044308 and DA018343).

Prenatal circadian rhythm disruption induces sex-specific substance use-related phenotypes in mice

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20% of Americans are at risk for environmental circadian rhythm disruptions (CRD) due to shift work. These individuals experience substantial negative health outcomes, but females are especially affected with greater vulnerability for substance use (SU) and adverse outcomes associated with pregnancy. These outcomes not only occur during pregnancy, but offspring are also affected at birth and later in life. Prenatal CRD (pCRD) in mice recapitulates these risks, increasing adverse pregnancy outcomes and altering behavior in adult offspring. However, it is unknown whether pCRD affects SU in mature offspring. C57Bl/6J dams were sham handled or disrupted, by reversing the light/dark cycle 4 times during gestation. Reward-related behaviors were measured in mature offspring. Contingency degradation was used to measure decision making. Mice were trained to respond on two levers for food, then the likelihood that one of those levers will be reinforced was degraded. Another cohort was trained to respond for food before jugular catheterization. After recovery, mice were trained to respond on another lever for cocaine. Acquisition, the reinforcing and motivational properties of cocaine, extinction and cue-induced reinstatement were measured. Interestingly, females exposed to pCRD developed an anhedonic-like phenotype with decreased food self-administration, cocaine intake and reinforcing properties of cocaine. On the other hand, males showed a SU-like phenotype with increased higher order food self-administration and cocaine reinforcement. Furthermore, male pCRD mice maintained goal-directed decision making, responding more on a reinforced aperture, while female pCRD mice did not, indicating habit formation. Together these results suggest that male and female mice exposed to pCRD respond differently for rewarding outcomes. The SU-like phenotype in male pCRD mice is likely driven by increased reinforcement or enhanced reward sensitivity, while the anhedonic-like phenotype in pCRD females is likely driven by decreased goal sensitivity. By understanding how disrupted rhythms during pregnancy affect SU vulnerability in mature offspring, we can develop novel therapeutic approaches for SU in adults.Funding Source: DA039865 (McClung), DA046117 (DePoy), NARSAD (DePoy)

MICE LACKING 5-LIPOXYGENASE DISPLAY MOTOR DEFICITS ASSOCIATED WITH CORTICAL AND HIPPOCAMPAL SYNAPSE ABNORMALITIES

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Lipoxygenase (5-LOX) is an enzyme essential for the synthesis of lipid inflammatory mediators-leukotrienes and lipoxins. It is widely expressed in immune system cells. However, recent reports suggest that central nervous system (CNS) neurons and glial cells also express high levels of 5-LOX, outside the context of inflammation, but the physiological role for 5-LOX in the CNS remains unclear. The aim of the present study was to explore the role of 5-LOX in microglial activation, synaptic plasticity and behavior. We used adult male 5-LOX knockout mice (5-LO-/-) and their wild-type (WT). We found that 5-LO-/- mice present increased repetitive behavior (evaluated with the marble burying test) but no alterations in memory function (measured by the novel object recognition/ passive avoidance tasks) or anxiety-like behavior (evaluated with the elevated plus maze task), as compared with WT. In addition, 5-LO-/- mice presented motor deficits (assessed by the Rotarod test), but no differences were observed in sensorial tests (Von Frey hair, formalin and hot plate). Associated with these results we observed increased levels of the synaptic proteins PSD95 and synaptophysin (assessed by Western Blot analysis) both in the motor cortex and hippocampus but found that BDNF expression was unchanged in the same brain areas. This increase in synaptic proteins led us to hypothesize a deficit in synaptic pruning. We used qPCR to analyze targets known to be involved in this process and found an increase in CX3CR1, along with a decrease in its ligand, CX3CL1, in the motor cortex of 5-LO-/- mice. Despite this disturbance in the CX3CR1-CX3CL1 axis, microglial morphology and density (as evaluated by IBA-1 immunostaining) were the same between the groups. Together, our results suggest that 5-LOX expression may be related to fine motor performance, repetitive behavior and changes in synaptic density. The absence of 5-LOX products may lead to altered microglia-neuron interactions, through the CX3CR1/CX3CL1 signaling axis, affecting microglial pruning. Funding: CNPq, CAPES, Faperj

Serotonin receptors 2A in the rat mPFC are necessary for Retrieval Induced Forgetting.

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Over the past several decades, neurobiological research on memory has been focused on the mechanisms underlying memory storage. Nevertheless, the study of forgetting and, specifically, active and selective forgetting has been increased since Anderson et al. showed in 1994 that the retrieval of certain memories could cause the forgetting of related, but not explicitly evoked information by a mechanism called retrieval-induced forgetting (RIF). Active forgetting occurs in many species, but how the mechanisms that control behavior contribute to determining which memories are forgotten is still unknown. We previously found that when rats need to retrieve particular memories to guide exploration, it reduces later retention of other memories encoded in that environment. As with humans, RIF in rats also relies on prefrontal control processes, is competition-dependent (only occurs when memories compete), and cue-independent (forgetting generalizes to a variety of cues). This work aims to explore if and how the serotonergic system participates in RIF using a task based on spontaneous object recognition. In particular, we used a pharmacological approach to manipulate the activity of the serotonin receptor 2A (5-HT2AR) in the rat medial prefrontal cortex (mPFC) specifically during the phase when memories compete. In different experiments, we used an antagonist of the 5-HT2AR (MDL 11,939), specific inhibitors for members of the Î²arr2 signaling pathway (LY 294002, PP2), and an agonist of the 5-HT2AR (TCB-2). We found that a 5-HT2AR antagonist and a PI3K inhibitor, which is part of the Barr2 pathway, impaired RIF but did not affect memory in other ways. Moreover, injection of TCB-2 promoted RIF in animals that would not normally forget. In summary, 5-HT2AR signaling in the rat prefrontal cortex is necessary for the occurrence of RIF and is partially reliant on the activation of the Barr2 pathway. Funding Acknowledgement: Agencia Nacional de Promoción Científica y Tecnológica (PICT 2015-2344, PICT 2018 1063)

Cannabis oil strain differentially impacts reward learning, decision-making, and impulsivity on a rodent gambling task.

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Cannabis is being legalized globally at increasing rates, making it pressing to understand how chronic exposure to cannabis perturbs decision-making and leads to addiction. Cannabis users make decisions on gambling tasks that lead to larger immediate gains and higher overall losses, suggesting users are prone to impulsive decision-making. Deficits among cannabis users have also been reported on measures of motor inhibition, risk-taking, and decision-making. Does impulsivity lead to cannabis consumption or does cannabis consumption aggravate impulsivity? Moreover, how are decision-making strategies different under the influence of cannabis sativa vs. indica? Methods: The impact of cannabis exposure on decision-making can be quantified using a validated rodent assay of cost-benefit decision-making: the rat Gambling Task (rGT). Long-Evans male rats (N=32) first learned to nosepoke at illuminated response apertures, and baseline scores of learning rate, attention and impulsivity were observed. Rats were then orally dosed with 3mg/kg THC from cannabis sativa, cannabis indica, or a vehicle-control solution 2 hours prior to each cued rGT test session for 25 days. Results: Rats treated with cannabis became significantly more impulsive than vehicle controls. Sativa-treated rats took longer than controls to learn the most optimal choice. Animals exposed to indica were more likely to be impulsive after a loss than a win, perhaps indicative of greater negative urgency. Sativa animals were more likely than controls to impulsively attempt to make risky choices. Conclusion: Group differences in impulsivity and learning rate were found after cannabis exposure. Cannabis sativa and indica, though thoroughly hybridized, have differing effects on learning, impulsivity, and decision-making â€“ effects that likely depend upon a wider variety of cannabinoids than delta-9-tetrahydrocannabinol alone. Funding: Canadian Institute of Health Research Grant awarded to C.A.W. UBC Institute of Mental Health Marshall Scholarship awarded to M.L.M

Inhibition of Parvalbumin Interneurons (PV INs) in the Prefrontal Cortex after Chronic Variable Stress (CVS) Mitigates CVS induced behavioral and physiological phenotypes in Male Mice

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Chronic stress leads to hypofunction of the prefrontal cortex (PFC), mechanisms of which remain to be determined. Enhanced activation of GABA-ergic of parvalbumin (PV) expressing interneurons (INs) is thought to play a role in stress induced prefrontal inhibition. In this study, we tested whether inhibition the activity of PFC PV INs after chronic stress can rescue chronic stress-related behavioral and physiological phenotypes. Mice underwent 2 weeks of chronic variable stress (CVS) followed by a battery of behavioral tests known to be affected by chronic stress exposure, e.g., an open field (OF)/ novel object recognition, tail suspension, sucrose preference (SPT) and light dark (LD) box. Inhibitory DREADDs were actuated by 3mg/kg CNO administered 30 min prior to each behavioral test. CVS caused hyperactivity in the OF, reduced sucrose preference in the SPT indicative of enhanced anhedonia, and increased anxiety like behavior in the LD box. Inhibition of PV IN after stress mitigated these effects. In addition, CVS also resulted in reduced thymus weight and body weight loss, which were also reversed by PV IN inhibition. Our results indicate chronic stress leads to plastic changes in PV INs preventing which may mitigate stress effects. Our behavioral and physiological findings implicate cortical GABAergic interneurons as a therapeutic target in stress related diseases such as anxiety and depression.

Aerobic exercise preserves pattern separation ability and enhances neurogenesis in a dietary model of obesity

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Excessive consumption of high fat and high sugar (HFHS) foods can not only cause weight gain and obesity but also reduce adult hippocampal neurogenesis. When neurogenesis is disrupted, pattern separation the process of keeping similar stimuli as distinct memory representations is impaired. The objective of this study was to determine whether exercise can improve pattern separation in mice fed HFHS diet via enhanced neurogenesis. Male and female C57Bl6 mice were fed either an HFHS diet (n=32) or a control diet (n=31) for 28 days and randomly assigned to either running wheel access for 3 hours 5 days a week, or no access. Memory was then tested on a spontaneous location recognition (SLR) task. SLR assesses pattern separation by the extent that mice can discriminate the locations of objects manipulated in the similarity of the distance between each other: dissimilar (ds-SLR), similar (s-SLR), or extra similar (xs-SLR). Markers of new neurons and neural stem cells were analyzed, and physiological measures of body weight, abdominal fat, and liver weight were collected. HFHS diet led to impaired memory under s-SLR conditions (high cognitive load) compared to control-fed mice. Male mice fed HFHS diet were impaired in d-SLR performance (low cognitive load) indicating severe impairment in overall spatial memory. In contrast, exercise prevented cognitive decline in HFHS-fed mice tested on d-SLR and s-SLR while also enhancing pattern separation ability in xs-SLR, irrespective of diet, in both males and females. Surprisingly, HFHS did not impact markers of neurogenesis, but behavioral improvements with exercise were accompanied by increased numbers of immature neurons and proliferating cells. Exercise reduced body and liver weight gain in HFHS-fed mice. Our results indicate that exercise can prevent diet-induced cognitive impairments in pattern separation, which corresponded with increased numbers of immature neurons. Exercise may be an intervention for preserving hippocampal function in obesity.

Social reciprocity is altered in mouse models of neurodevelopmental disorders in a naturalistic setting.

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Social behavior is altered in a range of psychiatric and neurodevelopmental disorders, with alterations ranging from social withdrawal to inappropriate social interactions. Characterizing such behavioral impairments and understanding their underlying causes can lead the way to better care and treatment for those affected. Unfortunately, many treatments developed in the lab fail to produce results in the clinic. In order to address to translation issue and to produce results generalizable to a wide range of contexts, behavior needs to be observed in conditions incorporating as many features of a natural environment as possible. Thus, we first characterize social interactions in wild-type mice (C57BL/6J) living in multi-female, mono-male groups hosted in a seminatural environment entailing an enriched open field and a burrow system. The behavior patterns observed were compared to that of mice presenting an ASD-like phenotype (Shank3B-/-) and that of inbred mice showing a natural deletion for the gene Disrupted in Schizophrenia-1 (129S4). By comparison to C57BL/6J mice, 129S4 mice showed a deficit in social reciprocation in the form of decreased allosniffing, and a loss of social interest represented by a reduction in anogenital sniffing. Interestingly, social approach was unaffected in 129S4 mice. Preliminary data from Shank3B-/- mice suggest that deletion of Shank3B made mice less socially attractive to their conspecifics. Additionally, 129S4 mice appeared less active compared to C57BL/6J and Shank3B-/-; while Shank3B-/- showed similar activity levels than Bl6 mice. Social repellence in Shank3B-/- likely results from their well-established social withdrawal and potentially from tactile hypersensitivity, a trait we will further investigate in future studies. To the contrary, the reduction in social behavior observed in 129S4 mice was more nuanced. Normal levels of social approach combined with a deficit in social reciprocation interestingly represent the complex abnormalities in social behavior sometimes displayed by patients with psychiatric conditions. These data together will give new insight on the abnormal modulation of social interaction in well-established models of neurodevelopmental and psychiatric disorder, using a naturalistic, translational approach.

The nicotinic acetylcholine receptor modulator AVL-3288 attenuates hippocampal-based cognitive deficits following repeated mild traumatic brain injury in adolescent rats.

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Sports-related concussion (SRC, a subset of mild Traumatic Brain Injury) in adolescents is a leading cause of long-term cognitive deficits. We developed an age-appropriate and clinically relevant model of SRC in adolescent male and female Sprague Dawley rats by subjecting them to 3 separate episodes of an impact to the intact skull (2.0mm depth at 5.5m/s velocity) over 7 days. Rats were tested for hippocampal-dependent memory at 1-and-4 weeks post-injury in the Morris water maze (MWM; female n=7/group 1 week and 4/group 4 weeks; male n=7/group 1 week and 8/group 4 weeks) and novel object location (NOL) task (female n=7/group 1 week and 8 sham, 11 injured 4 weeks; male n=8 sham, 9 injured 1 week; 8/group 4 weeks). At 1 week, only male brain-injured animals exhibited significant deficits in locating the submerged platform in the MWM (sex*injury p=0.0007) and recognizing the new location of an object in the NOL task (sex*injury p=0.013). However, male and female brain-injured animals exhibited deficits at 4 weeks in the MWM (injury p=0.000002) and NOL (injury p=0.000003) task. We hypothesized that impaired cholinergic transmission may be a mechanistic basis for these cognitive deficits. Positive allosteric modulation of nicotinic acetylcholine receptors (nAChR) via AVL-3288 was reported to diminish spatial learning deficits in moderately brain-injured adult male rats. Therefore, male and female rats underwent repeated mild injury or sham surgery in adolescence and then were injected with AVL-3288 at 30 minutes prior to testing the animals in either the MWM or NOL tasks at 4 weeks post-injury (female n=6/drug group, n=5/vehicle group; male n=6/group). Treatment with AVL-3288 attenuated injury-induced cognitive deficits in both tasks (treatment p=0.004 MWM, p=0.001 NOL) suggesting that reduced activity of the nAChR may underlie post-traumatic cognitive deficits. Funding provided by National Institutes of Health R01 NS110898 and Commonwealth Universal Research Enhancement from the Pennsylvania Department of Health SAP 410-007-7079.

Adolescent Binge Alcohol Exposure Impairs Spatial Learning and Memory in a Sex-Specific Manner in C57BL/6J mice

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Within the USA, ~50% of adolescents reported consuming alcohol by 12th grade. With alcohol readily available, it's consumption can increase risk of permanent detrimental changes to brain maturation and function, especially impairing learning and memory. We aimed to determine the sex-specific persistent effects of adolescent binge alcohol exposure on the acquisition and retention of spatial learning and memory. We exposed adolescent male and female C57BL/6J mice to intermittent ethanol vapor inhalation exposure (or air as control). Mice were exposed to repeated two day ON/two days OFF cycles from postnatal day (PND) 28-42, which is defined as adolescence in the rodent. We use this exposure model to study binge ethanol dosing in adolescent mice. On PND 45, mice began training using the Barnes Maze to determine their acquisition and performance of learning and spatial memory. The Barnes maze is a circular platform with 19 covered holes and 1 uncovered escape tunnel. Mice learn the location of the escape tunnel using spatial cues. Improved performance and acquisition of spatial learning is defined as the mice entering the escape tunnel more quickly. The training protocol consists of 1 habituation, 19 acquisition, and 4 probe trials. Several parameters were quantified including latency to locate and enter the escape tunnel and number of errors. Preliminary data indicate that male ethanol-exposed mice showed impaired spatial learning and memory compared to controls. Females showed a similar, but less robust trend. These data highlight important sex-specific effects of adolescent binge alcohol exposure on learning and memory. Together, these data may indicate unique long-term changes in learning acquisition that impact males and females differently, pointing to the importance of investigating other kinds of memory tasks. We are investigating this effect in other learning and memory tasks to better understand how different types of learning are impacted.Funding: NCATS NIH 5UL1TR002489-04

Acute environmental de-enrichment triggers severe aggressive behavior in BALB/c mice.

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Environmental factors crucially impact animal's behavior. During the process that animals live and cope with the ever-changing surroundings, functionally adapted behaviors are developed and socially maladaptive coping strategy may occur especially in negative and unescapable environments. To elucidate the biological mechanisms underlying such maladaptive coping behaviors is important for understanding depression and other psychiatric conditions of human. However, many results obtained from the laboratory experimental paradigms using rodent models are highly influenced by the human experimenters, thus hardly recapitulate the spontaneous components of animal's coping behaviors. Here we report that an acute environmental de-enrichment paradigm: moving BALB/c mice from a enriched environment housing with ample sensory, motor, and social stimulations to a standard laboratory housing, triggers severe fights among the animals that result in physical damages, disrupted circadian locomotion activities, and social distancing. It is noteworthy that BALB/c mice carry a genetic polymorphism that reduces the enzymatic activity of tryptophan hydroxylase in synthesizing serotonin. Given the important psychological role of serotonin, this new paradigm potentially represents a relevant laboratory paradigm for understanding behaviors in human populations at higher risk of stress-related disorders, especially under behavioral restriction.This research was financially supported by KAKENHI 19H04907, 19H05212, 21H02580, AMED 18dm0307023h 0001, Hirose research grant, and Takeda research grant to DOW, and KAKENHI 21J15696 to MS.

The role of progesterone in dorsal hippocampal D2-type dopamine receptor facilitated social learning in male mice.

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Social learning is an adaptive form of learning that may be defined â€œlearning that occurs via the observation of, or interaction with, a conspecific or it’s products (Heyes, 1994; Galef, 1998). By studying the social transmission of

food preference, previous researchers have implicated many systems and neurobiological mechanisms in social learning, including the dopaminergic system, the dorsal hippocampus (HPC), estrogens and more recently androgens. My recent work has focused on the role of progesterone in dorsal HPC D2-type dopamine receptor mediated social learning in ovariectomized female mice. Preliminary findings suggest that progesterone treatment prolonged the expression of the socially acquired food preference and reversed the impairing effects of intra-HPC D2-type dopamine receptor antagonism on social learning. However, the role of progesterone in the male brain during social learning has never been assessed, yet the male and female brain expresses similar progesterone receptor levels. Specifically, in male and female mice, progesterone receptor (PR) immunoreactivity was prominent in the CA1 region of the HPC, and discrete extranuclear PRs were distributed throughout the HPC formation in both neurons and glia (Mitterling et al., 2011). The present study elucidates whether, similar to females, progesterone modulates dorsal HPC D2-type dopamine receptor mediated social learning in male mice. To test this, adult castrated male â€œobserversâ€• (OBS) are implanted with either long-term subcutaneous slow releasing progesterone or vehicle pellets. They then receive acute bilateral infusions of the D2-type DA receptor antagonist raclopride (20 Âµg/ÂµL) into the dorsal HPC 10-minutes prior to a 30-minute social interaction with a recently fed, same-sex, familiar â€œdemonstratorâ€• (DEM). Immediately following the social interaction, OBSs undergo an 8-hour choice test where they have free access to two novel flavored food diets. If social learning occurs, the OBS prefers the DEM diet. As in our preliminary findings with ovariectomized females, it is predicted that progesterone treatment will counter the impairing effects of intra-HPC D2 antagonism on social learning in castrated males, further elucidating the hormonal regulation of the social brain. Funded by NSERC.

Rodent Behavioral and Antidepressant Effects of Psilocybin and Novel Tryptamines

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Clinical trials on the use of psilocybin to treat depression are promising, but still in preliminary stages. Additionally, they are confounded by the presence of hallucinations, which may not be necessary for its clinical effectiveness but create significant challenges in experimental design. Our research group recently began investigating the potential of other tryptamines related to psilocybin: norbaeocystin, aeruginascin, and baeocystin. In this study, we determined if these compounds cause hallucination- and antidepressant-associated behaviors in rats. When administered alone, baeocystin, norbaeocystin, and aeruginascin did not cause acute behavioral responses (i.e. head twitch response) in rats at any dose, implying it may not cause hallucinations. To determine the therapeutic potential of these tryptamines, we administered these compounds, vehicle, or a positive control of fluoxetine, via gavage in male Long Evans rats (n=10) where we used the forced swim test (FST) as a measure of antidepressant efficacy for these tryptamines. Similar to fluoxetine, we found that rats given these tryptamines had significantly decreased durations of immobility in comparison to our negative control rats in the FST (p<.05). Combined, these results suggest these tryptamines may have strong potential as an antidepressant alternative to modern antidepressants. Future studies will validate these effects in other behavioral models and investigate biomarkers of antidepressant activity, such as hippocampal BDNF expression. Funding for this project was provided by PsyBio Therapeutics, Inc.

The rapid effect of estrogens on social recognition in the paraventricular nucleus of male mice.

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Estrogens and oxytocin (OT) both mediate social recognition (SR), as shown by studies where knocking out the genes for the estrogen receptors (ERs), OT, or the OT receptor (OTR) impairing SR and studies where administrations of 17b-estradiol (E2), ER agonists, or OT facilitated SR. It has been hypothesized that estrogens and OT interact to mediate SR and that this interaction occurs by estrogens binding to the ERs in the paraventricular nucleus of the hypothalamus (PVN) to facilitate the production and release of OT. The OT will then

reach the medial amygdala (MeA) and bind to the OTR. The MeA also receives projections from the olfactory bulbs, so the model suggests that it is the OT binding to the OTR in the MeA that allows the incoming olfactory information to be used to recognize a familiar individual. We have previously tested this model and if it occurs through estrogensâ€™ rapid mechanisms. We found that SR could be rapidly facilitated by infusions of E2 into the PVN and that this rapid facilitation of SR could be blocked by also infusing an OTR antagonist into the MeA. These findings showed support for the model and that it occurs through estrogensâ€™ rapid mechanisms. However, this was only conducted in ovariectomized female mice, so we are currently investigating whether this E2/OT interaction also occurs in males. Castrated male mice receive infusions of E2 into the PVN and are tested in a rapid SR paradigm. In this paradigm, two same-sex stimulus mice are presented in two 5-minute sample phases, followed by a 5-minute test phase, where one of the stimulus mice is replaced with a novel mouse. If the novel mouse is investigated more than the other, it indicates the familiar mouse is recognized. The paradigm takes place within 40 minutes of infusion to test the rapid mechanisms of estrogens. We have found that 25, 50, and 100nM doses of E2 in the PVN do not rapidly facilitate SR in male mice. However, it is possible that an effective dose for males is outside of this range, found to be effective in females, so two additional doses are being tested (10nM and 200nM). If these doses also show no facilitating effects, it would suggest that E2 in the PVN of male mice does not rapidly facilitate SR and that the estrogen/OT interaction occurs in female but not male mice. Funded by NSERC.

Social buffering reduces LPS induced neuroinflammatory distress-associated behaviors in mice

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The increase of lipopolysaccharide (LPS) concentration in the brain leads to neuroinflammation, a major determinant for cognitive impairment in many neurodegenerative diseases (Ransohoff, 2016; Zhao, 2019). Levels of LPS in the gut flora can be correlated with LPS levels in the central nervous system in patients with schizophrenia, Parkinson's disease, and Alzheimer's disease (Bhattacharyya, 2020). Here we studied the effects of systemic LPS injection (e.g., to mimic intestinal infection) on behavior.We first asked if and how much LPS would enter the central nervous systems after systemic injection. We used LPS conjugated to a far-red emitting dye (Cy5.5), and imaged LPS trafficking from the gut to the nervous system in live C57Bl6, albino, and nude adult mice. To optimize imaging from the abdominal region, mice were fed a diet without chlorophyll to decrease autofluorescence. After clearing autofluorescence, mice were injected with a LPS-Cy5.5 (N=5) or saline (N=5). In the periphery, we found that the LPS localized in the spleen, kidney, and colon. We also found that conjugated LPS could pass the blood-brain barrier and accumulated in the hippocampus. We then asked how LPS injection affected overall behavioral profiles of isolate and socially-housed mice, using a system we developed for continuous 24/7 behavioral monitoring and neural recording (Carcea et al. 2021). Mice demonstrated a range of sickness behaviors (Hart, 1988) including reductions in arousal level, less time spent foraging, and significant time spent hunched over. Continuous video for 24 hours pre-injection and over 72 hours post-injection was scored for LPS-injected socially-housed mice in which one of the two animals was injected (N=5), compared to saline-injected socially-housed controls (N=3), LPS-injected singly-housed mice (N=6), and saline-injected singly-housed mice (N=3). We found that co-housing an infected mouse with a healthy conspecific reduced mortality and shortened the duration of expressed sickness behaviors. Thus LPS might enter the brain to direct impact neural processing and behavior, interacting with internal state factors that might be positively regulated by social buffering or social interactions.

Correlation Between Refugee Post Migration Stress And Breast Cancer Awareness and Screening Attitudes in a Sample of Syrian Refugee Women Resettled in Houston, Texas, USA

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Breast cancer is the most-commonly diagnosed cancer and the second-leading cause of cancer death among women in the United States (US). While early detection and treatment effectively reduce morbidity and mortality associated with the disease, breast cancer cases are expected to rise because of COVID-19-related treatment delays and lack of screening. This is particularly concerning for refugee women, who are less likely to undergo screening due to poor health literacy and other factors. Displaced Syrians are one of the largest refugee populations in the world. More than 20,000 Syrian refugees are resettled in the US. Houston, Texas is an active

refugee resettlement city, hosting ~300 Syrian refugee families. Psychological trauma and the practical challenges of displacement make preventive health practices negligible, with women being the most vulnerable. A pilot study was conducted to investigate the association between migration stress and breast cancer awareness and screening attitude. In the present sample, 50% of Houston-based Syrian refugee women (N=42) reported biased attitudes towards general health check-up, exhibited limited breast cancer knowledge and awareness, and experienced elevated barriers to mammogram screening according to the validated Breast Cancer Screening Beliefs Questionnaire (BCSBQ). Interestingly, salivary cortisol and mitochondrial DNA (mtDNA) levels were significantly elevated in Syrian refugee women than in Arab community control samples, suggesting higher physiological stress among refugee women. Additionally, Syrian refugee women (N=55) endorsed higher perceived stress and elevated mental health risk than Syrian refugee men (N=38) in Refugee Post Migration Stress Scale (RPMSS) and Afghan Symptom Checklist, respectively. Significant correlations were observed between BCSBQ and RPMSS, indicating the association/correlation between elevated psychological stress and low breast cancer literacy and screening behaviors. Despite the small sample size and the cross sectional design, the present work illustrates emerging evidence aligned with/supporting the previously documented connection between psychological stress and the susceptibility to develop breast cancer.

Epigenetic mechanisms underlying susceptibility to methamphetamine self-administration in methamphetamine-sired male rats.

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Preclinical evidence indicates parental exposure to drugs of abuse alters behavior and physiology of offspring. We previously demonstrated that when male rats self-administered cocaine, their male, but not female, progeny displayed reduced cocaine self-administration. Whether this drug resistance is similar in the offspring of sires who self-administer other psychostimulants, such as methamphetamine, has not yet been explored. Here, we tested the hypothesis that male, but not female, offspring of methamphetamine self-administering sires would self-administer less methamphetamine than saline-sired conspecifics. Sires self-administered methamphetamine and controls received yoked-saline delivery for 60 days and were mated with naÃ¯ve females. Adult F1 offspring were allowed to lever press for intravenous methamphetamine (0.1 mg/kg/inf) for 10 days on a fixed ratio 1 schedule. After two days on a fixed ratio 5 schedule, motivation for methamphetamine was assessed using a progressive ratio schedule. Surprisingly, relative to saline-sired rats, male methamphetamine-sired offspring self-administered significantly more methamphetamine. Motivation for methamphetamine was also higher in methamphetamine-sired vs. saline-sired male offspring. There was no difference in methamphetamine self-administration or motivation for methamphetamine in female offspring. The gene expression and open chromatin profiles of experimentally-naÃ¯ve methamphetamine- and saline-sired male offspring were interrogated by single cell RNA-sequencing and ATAC-sequencing of the nucleus accumbens. These results suggest paternal methamphetamine use may confer increased drug taking in male offspring via epigenetic inheritance. Future experiments will interrogate the epigenetic profile in sperm of methamphetamine sires for targets that may influence offspring gene expression. Supported by NIH grant R01 DA033641.

The automated social operant task: a quantitative measure of social motivation in mice.

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Humans and mice are social creatures, finding social interactions inherently rewarding. Social motivation, the processes that drive social interactions, is a keystone of development and is hypothesized to underlie social deficits in Autism Spectrum Condition (ASC). Social motivation is encompassing multiple components, including social reward and social orienting. Many tasks exist to assay general socialization yet social motivation assays are limited. Thus, we adapted standard operant conditioning into an automated social operant assay, rewarding nosepokes with opportunity for transient social interaction. We directly quantify social motivation by increasing the number of nosepokes (work) required for a reward. Simultaneously, social orienting is assessed with automated tracking. We established that C57 mice will work for access to a social interaction, increased relative to work for

access to an empty chamber, and will orient to a social stimulus. We found that individual motivation level is stable across testing days, and interestingly, that male mice display higher motivation than females. Then, we validated the assay with two test cases. Using the Shank3b knockout (KO) mouse ASC model, we demonstrate reduced social reward-seeking in Shank3B KOs and reduced social orienting in male Shank3B KOs. In line with oxytocinâ€™s role in social reward circuitry, we show that administration of oxytocin antagonist reduces social motivation. Overall, this social operant assay provides a newly validated tool for more thorough assessment of normal social development, social deficits in mouse models, and mapping social motivation brain circuits.
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Participation of the neurodevelopmental disorder associated gene MYT1L in motor function and sensory responsivity.

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Putative loss-of-function variants in the gene Myelin Transcription Factor 1-like (MYT1L) located on chromosome 2p25.3 have been associated with a variety of neuropsychiatric and behavioral features including intellectual disability (ID), autism spectrum condition (ASC), attention-deficit hyperactivity disorder (ADHD), hypotonia, motor and speech delays, and obesity. However, little is known about the function of MYT1L or how it participates in behavioral circuits. To better understand MYT1L function in vivo and the impact of its loss on behavioral outcomes, we generated a novel mouse model of Myt1l haploinsufficiency by mimicking a frameshift mutation observed in an index patient with ID, ASC, ADHD, obesity, and developmental delays. Previously, we showed our model recapitulates several clinical features of MYT1L Syndrome including obesity, strength impairments, social deficits, and hyperactivity. In the current study, we extended our investigation to understand motor function and sensory responsivity in the presence of Myt1l haploinsufficiency by examining gait development, motor coordination, visual acuity, tactile sensation, olfactory function, and thermal sensation. We observed alterations in motor coordination, tactile discrimination, and sex-specific cold and heat sensitivities. Together, our current data suggest that MYT1L plays a role in motor and sensory functions, which may be sex-dependent. The recapitulation of clinical features in this model will allow us to next dive deeper into examining how MYT1L participates in behavioral circuits (both spatially and temporally), and in what manner, genetically and pharmacologically, we can rescue or ameliorate these behavioral difficulties. Funding Support: The Jakob Gene Fund (JDD,SEM), NIMH (R01MH124808, JDD,SEM), and NICHD (P50HD103525, IDDRC@WUSTL).

Age- and sex-related changes in short and long-term plasticity at the perforant path-dentate gyrus synapse in adult, and old-adult Sprague Dawley rats

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The primary input into the memory structure, the hippocampus, arises from the principal neurons in the entorhinal cortices. The medial entorhinal projection to the dentate gyrus (DG) was the synapse first implicated in plasticity studies, and despite the known relevance of these regions in Alzheimerâ€™s disease, surprisingly few studies have examined normal age- and sex-dependent changes in plasticity at this synapse. We examined the effects of normal aging of the medial perforant path input into the DG in adult (5-9mo) and aged (18-20mo) urethane anesthetized male and female rats, examining current intensity profiles interwoven with paired pulse facilitation (PPF) and inhibition (PPI), before and after a moderate burst long-term potentiation (LTP) protocol. Female rats possessed higher baseline levels of granule cell excitability than male rats (population spike, mV) however, no differences were observed in the baseline response of the synaptic component (EPSP slope; mV/ms). Although

female rats continued to express larger absolute population spike measures in the post-tetanic record, normalization of data revealed larger %-increases of population spike in younger male rats. We suggest the decreased percentage change in females may be due to ceiling effects, and emphasize the relevance of reporting both absolute, in addition to percentage data. The main mechanism supporting spike LTP in adult male rats appears to be increased EPSP-Spike (E-S) coupling. In female rats, spike potentiation was predicted by early (0-30min post-LTP) EPSP slope increases, an effect not observed in male rats. Thus, EPSP slope changes appear to support spike changes in female rats but not males, while increases in E-S coupling support potentiation in adult males. Aged males show the lowest levels of plasticity. An analysis of NMDA currents during tetanic stimulation, and in the post-LTP record, revealed the highest NMDA contribution in young male rats during the initial delivery of LTP trains. Paired pulse analyses reveal that post-LTP female rats also show increased network excitability with higher levels of PPF (70ms ISI), and decreased GABA-B mediated PPI (120ms ISI). Funding Source: Alzheimer Society of Canada & Natural Science and Engineering Research Council- Discovery (SGW)

Age- and sex-specific changes in behaviour and hippocampal plasticity in young and aged, male and female rats after locus coeruleus originated tau dysfunction initiated in young adulthood.

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Abnormally phosphorylated tau, a protein implicated in Alzheimer (AD) pathology, has been identified in the noradrenergic locus coeruleus (LC) neurons of young adults (Braakâ€™s pretangle Stages a-b). The abnormal, but still soluble tau protein progresses to modulatory regions (Stage c), then to temporal lobe structures (Stages 1a/b). To model Braakâ€™s progression of pretangle stage tau dysfunction, we infused the LC of 3-mo old male and female TH-Cre rats with an AAV vector and transgene for a pseudophosphorylated human tau (htauE14-eGFP) or control (GFP-only or vehicle). Rats were tested for spatial memory (water maze) and odour discrimination at 1-3mo (young adult) or >12-mo (aged) post LC-htau infusion. Deficits in the acquisition of the water maze task were found selectively in male LC-htau rats (young and aged). The aged males also had deficit in difficult odour discrimination memory (two similar odourants). Dishabituation tests revealed aged htau males were impaired compared to control males in detection of the two difficult odorants. At 1.5mo post LC-htau infusion, htau-eGFP was colocalized in up to 98% of LC neurons in htau infused rats, and there was spread to raphe and entorhinal cortex. At 1-3 and >12-mo post LC-htauE14 infusion we examined the effects of LC-htau on beta-adrenoceptor dependent plasticity in the dentate gyrus (DG) using an in vivo, long-term potentiation (LTP) protocol. At 1.5mo post LC-htau infusion, potentiation of the DG-PP evoked population spike was reduced in LC-htau male rats compared to controls. LTP results in aged male rats were less conclusive due to decreased levels of potentiation in aged control males (see also Walling et al. IBNS, submitted). Aged female LC-htau rats possessed decreased potentiation of the population spike relative to control females. The results suggest that LC htau spreads to brain areas as predicted by Braakâ€™s pretangle stage AD and deficits in hippocampal plasticity are most evident in male LC-htau infused rats, with concomitant behavioural and cognitive deficits.Funding: Alzheimer Society of Canada (SGW)

Age-dependent alterations in touchscreen-based assessments of cognitive function in marmosets.

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Alzheimer's disease (AD) is a neurodegenerative disorder marked by progressive cognitive decline, and for which there is no cure. The primary risk factor for AD is chronological aging, and the ability to decipher between cognitive declines related to healthy aging versus impairment as a result of early prodromal AD is crucial for diagnosis, treatment, and prevention. Importantly, animal models that can best recapitulate the divergence of aging-related changes in humans are critical for supporting translational studies of potential novel therapeutics. Common marmosets (Callithrix jacchus) exhibit many aging-related changes similar to those observed in humans including cognitive decline. The purpose of the present studies was to establish and validate a testing battery sensitive to detecting an age-dependent cognitive decline in aging marmosets. Young (1-2 years of age) and aged (7-11 years of age) sex-matched marmosets were initially trained on an FR-1 schedule of positive reinforcement (20% marshmallow juice reward) using touchscreens mounted to their homecages. Upon meeting acquisition criteria, the DMTP task was introduced in which a visual cue (sample) was presented in 1 of 2 positions on the screen. After the delay period, the same visual cue was presented in both locations with responses to only the correct position

rewarded. At the conclusion of delay threshold testing for DMTP, the DNMTP task was introduced in which the same visual cues were used but the position opposite to the sample was rewarded. As expected, individual marmosets demonstrated delay-dependent reductions in accuracy. There was a significant effect of age in DNMTP with aged marmosets demonstrating increases in trials to meet criteria relative to young marmosets. Given the genetic heterogeneity and phenotypic diversity in marmosets, these data indicate a need for longitudinal within-subject analysis similar to what is required in humans in order to assess the contributions of biological aging to cognitive decline. Ongoing studies include additional touchscreen cognitive assessments and evaluations of our colony of PSEN1 marmosets and their age-and sex-matched WT controls. Funding for these studies is supported by NIA R24AG073190.

Effects of Adolescent Lorazepam Exposure on Drinking Behavior in Adulthood

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Benzodiazepines (BZDs) are strong anxiolytic drugs that act at GABA receptors, resulting in overall inhibition of the CNS. Benzodiazepines are one of few drugs that can be both prescribed by a doctor, but also recreationally abused. One in five high schoolers report using benzodiazepines either medically or recreationally. However, the longitudinal effects of benzodiazepine use during adolescence have not been well-investigated. The purpose of this experiment was to determine the effects of benzodiazepine exposure during adolescence on immediate stress levels and later adult alcohol self-administration in rats. A total of 48 rats (N=12/sex/group) were used in the experiment. During adolescence (Postnatal days [PNDs] 30-50), they received injections every other day of lorazepam (BZD group) or saline vehicle (control group). Open Field and Elevated Zero Maze protocols were used throughout the experiment to assess anxiety-like behavior of the subjects. From PNDs 100-141, the subjects underwent a two-bottle choice alcohol self-administration paradigm for four hours (8PM-12AM) every night during their dark cycle. On PND143, the subjects were given an intraperitoneal injection of 42% ethanol (1 mg/kg). An hour later, they were sacrificed and perfused for tissue collection. The tissue was stained for neural activity using C-Fos immunohistochemistry in the VTA and the NAc. OFT and EZM results showed that there was a significant difference in anxiety-like behaviors between the two groups, particularly on PND52, when the experimental group would be going through withdrawal. Ethanol self-administration results showed that adolescent exposure to BZDs increased adult alcohol intake and preference, but only in females. Preliminary results of C-Fos staining indicate that the BZD-exposed females exhibited higher neural activity under the influence of alcohol. Overall this project suggests that BZD use in adolescence has long term consequences, particularly in females, which urges reevaluation of industry prescription and regulation standards for these drugs. Funding Acknowledgement: N/A

Impact of melatonin deficit on the emotional status and oxidative stress-induced changes in sphingomyelin and cholesterol level in young adult, mature, and aged rats

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The pineal gland regulates the aging process via the hormone melatonin. The present report aims to evaluate the effect of pinealectomy (pin) on behavioral and oxidative stress parameters in young adult, mature and aging rats. Sham and pin rats aged of 3-, 14- and 18-months were tested in behavioral tests for motor activity, anxiety and depression. Oxidative stress was explored in the hippocampus by ELISA tests. The sham rats exhibited a decline of motor activity and increased anxiety with aging. Pin rats aged 3-months had elevated motor activity and decreased anxiety compared to the sham group. Pinealectomy did not affect the emotional response in mature and old rats. Pinealectomy induced depressive behavior in the youngest rats but not in aged rats. In mature rats, age-related oxidative stress was observed in the sham groups with increased lipid peroxidation and adaptive superoxide dismutase (SOD) activity. Age-dependent effect of melatonin deficit was detected on sphingomyelin (SM) level in the hippocampus and cholesterol levellipid profilen serum. Pinealectomy enhanced oxidative stress

through diminishing antioxidant capacity and increasing the MDA level in the hippocampus of 14-month-old rats. Our findings suggest that the impact of melatonin deficiency on emotional responses and oxidative stress in the hippocampus is age-related. However, there is no direct link between the age-associated effect of pinealectomy on behavioral responses and oxidative stress-induced changes in SM level in the hippocampus and lipid profile. Keywords: Age, Melatonin deficit, Anxiety; Depressive-like behavior, Oxidative stress, Rat. Acknowledgments This work was supported by the National Science Fund of Bulgaria (research grant # КП -06-ПН41/1).

The Cocaine and Oxycodone Biobanks: Two repositories of biological samples from genetically characterized outbred rats that exhibit compulsive-like escalation of cocaine or oxycodone self-administration

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Identification of the mechanisms that underlie compulsive cocaine or oxycodone use in animal models is a major goal for understanding the genetic risk factors for addiction and facilitating the identification of novel druggable targets. A key issue for the field is the lack of a repository that contains biological samples from behaviorally and genetically characterized rats. We introduce the Cocaine Biobank (www.cocainebiobank.org) and the Oxycodone Biobank (www.oxycodonebiobank.org), two repositories of biological samples from a unique, genetically diverse strain of outbred heterogeneous stock (HS) rats that have been behaviorally and genetically characterized using next-generation sequencing, state-of-the-art behavioral screening, and a variety of preservation techniques. Male and female rats are trained to self-administer cocaine (0.5 mg/kg/inf) in daily 6 h sessions or oxycodone (0.15 mg/kg/inf) in daily 12 h sessions and tested using progressive-ratio responding, responding despite adverse consequences (contingent footshocks), and measures of analgesia, hyperalgesia and irritability-like behaviors. Results show high individual variability with vulnerable and resistant rats that is likely to facilitate the detection of gene variants and the molecular and cellular mechanisms of addiction. Preservation techniques include perfusion, snap-freezing, and cryopreservation maximize the compatibility of these tissue banks with cellular, molecular, and anatomical methods. The Biobanks provides free access to over 20 organs. The Biobanks have the potential to facilitate identification of novel druggable targets and provide a unique data/tissue repository that will facilitate follow-up and replication studies.Funding: NIDA

Amphetamine increases motivation in humans and mice although did not affect the parietal alpha biomarker.

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Translating drug targets from preclinical models to phase III trials has proven difficult. Cross-species quantitative behavioral tasks enable greater validation of drug effects, but evidence for brain-based engagement during task performance would strengthen findings of cross-species experiments. Progressive ratio breakpoint tasks (PRBT) can measure motivation-like behavior in humans and rodents. Clinically, people with schizophrenia exhibit a reduced breakpoint. We recently described a cross-species electroencephalographic (EEG) biomarker: elevated parietal alpha power in humans and mice peaking before breakpoint. Given that amphetamine (AMP) increases breakpoint in mice, we tested whether AMP would increase breakpoint in humans as well, and if any changes would be seen in EEG biomarker. 23 healthy participants (52%M) were tested in PRBT with EEG after AMP (10 or 20 mg) or placebo. Male and female mice were trained on a rodent version of PRBT with EEG (n=28, 54%M) and treated with AMP (0.1,0.3, or 1 mg/kg) or vehicle. Another cohort of mice was trained on PRBT without EEG (n=15, 47%M) and treated with AMP (0.1 or 0.3) or vehicle. In humans, AMP increased breakpoint (p<0.005). In mice, the highest dose AMP significantly decreased breakpoint (p<0.001). No effect of AMP on alpha power was

observed in humans (p=0.402) or in mice (p=0.750). The untethered mice did not show a main effect of AMP, but showed a slight increase in breakpoint in those with low baseline (p=0.052). AMP increased the breakpoint of humans and low performing mice, but not EEG-tethered mice. Consistent with prior reports, elevated parietal alpha power was observed in humans and mice during PRBT. No effect of AMP on parietal alpha EEG was observed in either species. Current methods of EEG in mice may limit its use as a drug-sensitive assay of effort. Although these results raise doubt on the utility of parietal alpha power as a drug-sensitive effort marker in the PRBT, they do support the pharmacological predictive validity of the PRBT as a measure of effort in humans and mice. This work was supported by NIMH UH3MH109168.

Paternal methamphetamine administration does not cause such serious effects on rat offspring during development and in adulthood as maternal administration

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Methamphetamine (MA) is one of the most abused psychostimulants in the Czech Republic and worldwide. Previous studies have demonstrated the adverse long-term effects of maternal drug abuse on rat offspring. However, the father's contribution as a parent and donor of half the genetic information is unclear. The present study aimed to examine the effect of MA administration on male sexual behavior and the paternal MA exposure on behavioral development and locomotor activity in rat offspring. MA or saline (SA) was administrated to adult male rats in a dose 5mg/kg (s.c.) daily for period of 30 days. First, the effect of MA on sexual behavior and spontaneous locomotor activity (Laboras) of adult male rats was examined. Second, the impact of paternal MA exposure on rat pups was investigated using behavioral tests during development and locomotor activity tests in adulthood. Prior to testing, adult offspring were exposed to an acute challenge dose of MA (1 mg/kg) to examine the possible sensitizing effect of the paternal treatment. Our results demonstrated that MA administration does not affect sexual behavior. The data from Laboras showed that MA exposure has a significant effect on locomotor activity only in the case of acute MA application. As a matter of paternal administration effect on offspring, there were no significant differences in behavioral development or locomotor activity in adulthood. Further, our results demonstrated a significant increase in locomotor activity on the Laboras test after acute MA application. When comparing sex differences, females showed more activity than males in adulthood, whereas males were more active during development. In conclusion, in contrast to the maternal MA administration, our results show that paternal MA administration does not affect behavior during development and in adult offspring as it was shown after maternal administration. Nevertheless, our study is the first to determine the father's role as a parent and donor of half the genetic information on the effect of MA on rat offspring.Financial support: Research program Cooperatio Neurosciences, Progres Q35, and project PharmaBrain CZ.02.1.01/0.0/0.0/16_0250007444.

Sex differences in dopaminergic regulation of risky decision making.

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Risky decision making involves the ability to weigh risks and rewards associated with options to make adaptive choices. Impairments in this process are implicated in psychiatric conditions such as substance use disorders. Dopaminergic neurotransmission modulates risky decision making (risk taking) in males by acting on brain regions within the mesocorticolimbic circuit, such as the basolateral amygdala (BLA). Given that there are sex differences in risk taking, it is prudent to determine whether similar dopaminergic mechanisms are involved in female risk taking. To do this, male and female rats were trained in the Risky Decision-making Task (RDT) in which rats choose between a small, safe food reward and a large, risky food reward that is accompanied by an increasing risk of mild footshock punishment. In Experiment 1, rats were trained in the RDT and then received systemic injections of the D2 dopamine receptor (D2R) agonist bromocriptine prior to RDT testing. Bromocriptine decreased lever pressing for the large, risky reward in both male and female rats, but affected choice behavior in females at lower doses that were ineffective in males. To determine the neural substrate underlying such sex differences, rats in Experiment 2 were trained in the RDT and then received intra-BLA infusions of the D2R agonist quinpirole prior to RDT testing. Intra-BLA infusions of quinpirole decreased choice of the large, risky reward (decreased risky choice) in females, but had no effect in males. Further, this reduction in risky choice in females was accompanied by an increase in sensitivity to punishment. In the final experiment, rats received intra-BLA infusions of the D2R

antagonist eticlopride prior to being tested in the RDT. Eticlopride had no effect on risky choice in male or female rats. Considered together, these data indicate that sex differences in risk taking may be due to differential D2R sensitivity in the BLA, with greater sensitivity in females contributing to phenotypical female risk aversion. Future experiments will investigate the role of D1 dopamine receptors in the BLA in risk taking in males and females. Supported by NIDA R00DA041493-3.

Chronic stress impairs working memory in young adulthood but enhances working memory in aging.

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Normal aging is associated with varying degrees of memory loss coupled to differences in function of the hypothalamic-pituitary-adrenal (HPA) axis, the brain-body system involved in regulation of stress responses. Working memory, which depends on the prefrontal cortex (PFC), is susceptible to decline with age. Further, PFC neurons regulate HPA axis activity and undergo structural changes when challenged with prolonged exposure to stressful stimuli. Thus, we hypothesized that chronic stress would accelerate age-related working memory impairment and reveal mechanisms by which HPA axis dysfunction contributes to brain aging. To test this hypothesis, we evaluated PFC-dependent working memory in male or female F344 rats at 6, 14, or 24 months (mo) of age. Working memory accuracy was measured using a delayed match-to-sample (DMTS) operant task and, while testing was ongoing, similar numbers of each sex and age were assigned to unstressed (UNS) or chronic variable stress (CVS) treatment. CVS entailed twice-daily exposure to stressors that included forced swims, physical restraint, predator urine, or cage-flood, presented in an unpredictable order for 21 days; UNS rats underwent daily testing but were not exposed to stressors. We observed that CVS interacted with age and sex to influence working memory accuracy. In 6 mo males, CVS significantly reduced accuracy whereas CVS significantly enhanced accuracy of 14 and 24 mo males, compared to age-matched UNS. Choice accuracy of females was significantly greater compared to males, independent of age, but not observed to decline with age or stress. In parallel to effects on choice accuracy, CVS, older age, and female sex were all significantly associated with fewer completed trials. CVS also reduced body weight and increased adrenal weight, typical stress-associated physiological changes, regardless of sex or age. These findings reveal that multi-directional consequences of chronic stress on PFC-dependent working memory are highly dependent on biological sex and chronological age. Forthcoming studies will probe the cognitive, physiological, and molecular bases of these changes. With support from NIH Grant K01AG061263.

Cannabis extract alone and in combination with cannabidiol reduces relapse to methamphetamine and Locomotor sensitization.

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Methamphetamine (METH) is an addictive stimulant associated with severe health problems, with poor available treatments. We have previously demonstrated that cannabidiol (CBD) reduces relapse to METH seeking behaviour and METH-induced sensitization. Here we tested the ability of Goo (cannabis extract), and its combination with CBD, to reduce METH/sucrose relapse, METH induced sensitization, and the rewarding properties of Goo. In Experiment (Exp.) 1, twelve adult male Sprague-Dawley (SD) rats underwent a modified behavioural sensitization protocol where they received 7 daily METH injections (5mg/kg; i.p.). After withdrawal period, locomotor changes were examined over 4 challenge days where Vehicle (VEH), CBD (80mg/kg), Goo (43.5mg/kg), CBD+Goo were given 30 mins prior to METH challenge (1mg/kg i.p.), then locomotor activity was measured for 60 mins. In Exp. 2, twenty adult male SD rats were trained to intravenously self-administer METH via lever press during 2 hr sessions on a fixed ratio 1 schedule of reinforcement, then progressed to extinction (lever presses were no longer reinforced). Relapse-reducing effects of the treatments were tested in a series of METH-primed reinstatement sessions and administered as per Exp. 1. In Exp. 3, sixteen male SD rats underwent the same procedures as per Exp. 2, but they lever pressed for oral sucrose instead, in 30 mins sessions. Cannabinoids were tested as mentioned above. In Exp. 4, Forty-eight SD rats underwent conditioned place preference (CPP) paradigm (3 days of preconditioning, 6 days of conditioning, 1 final test day). CBD and

CBD+Goo treatment decreased METH-induced locomotor sensitization. All the treatments reduced METH relapse, but the combined treatment was more effective than CBD alone. Treatments had no effect on sucrose relapse. No cannabinoids showed rewarding properties. This is the first study to analyse the effect of a cannabis extract alone and supplemented with CBD and suggests that the combination of cannabis extract constituents offer treatment potential for METH use disorder better than those provided by CBD alone.