SOCIETY FOR NEUROSCIENCE

Michigan Chapter

53rd Annual Meeting

June 9, 2023
Brody Hall

Michigan State University

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2023 Meeting Schedule

8:30-9:00	Registration (Brody Hall Foyer)
9:00-10:15	Poster Session A (Brody Hall 134, 136, 138)
10:15-10:45	Break (Group B put up posters)
10:45-12:00	Poster Session B (Brody Hall 134, 136, 138)
12:00-1:00	Lunch (Brody Square)
1:00-2:00	Business Meeting (Brody Auditorium)

Welcome & President's Report; Treasurer's Report; Elections

To be elected during the meeting (self-nominations are welcome)

President-Elect (2023 – 2024)

Secretary (2023 – 2025)

Website Coordinator (2023 - 2025)

WSU Counselor (2023 – 2025)

WMU Counselor (2023 - 2025)

Counselor at Large I (2023 - 2025)

Student Counselor II (2o23 - 2025)

2:00-2:20	**Founder's Award Speaker: Sierra Boyd** *"Developmental exposure to the Parkinson's disease-associated organochlorine pesticide dieldrin increases dopamine release in the striatum in the a-synuclein pre-formed fibril mouse model"*
2:20-2:40	**Founder's Award Speaker: Carlye Szarowicz** *"Engaging the role of personalized medicine: impact of the rs6265 SNP in host and donor on dopamine neuron transplantation in Parkinson's Disease"*
2:40-3:00	Break
3:00-4:00	**Keynote Speaker: Dr. Greg Scherrer** *"The neurobiology of pain experience and its modulation by opioids"*
4:00-4:30	Awards and Adjournment

Michigan Chapter of the Society for Neuroscience Council

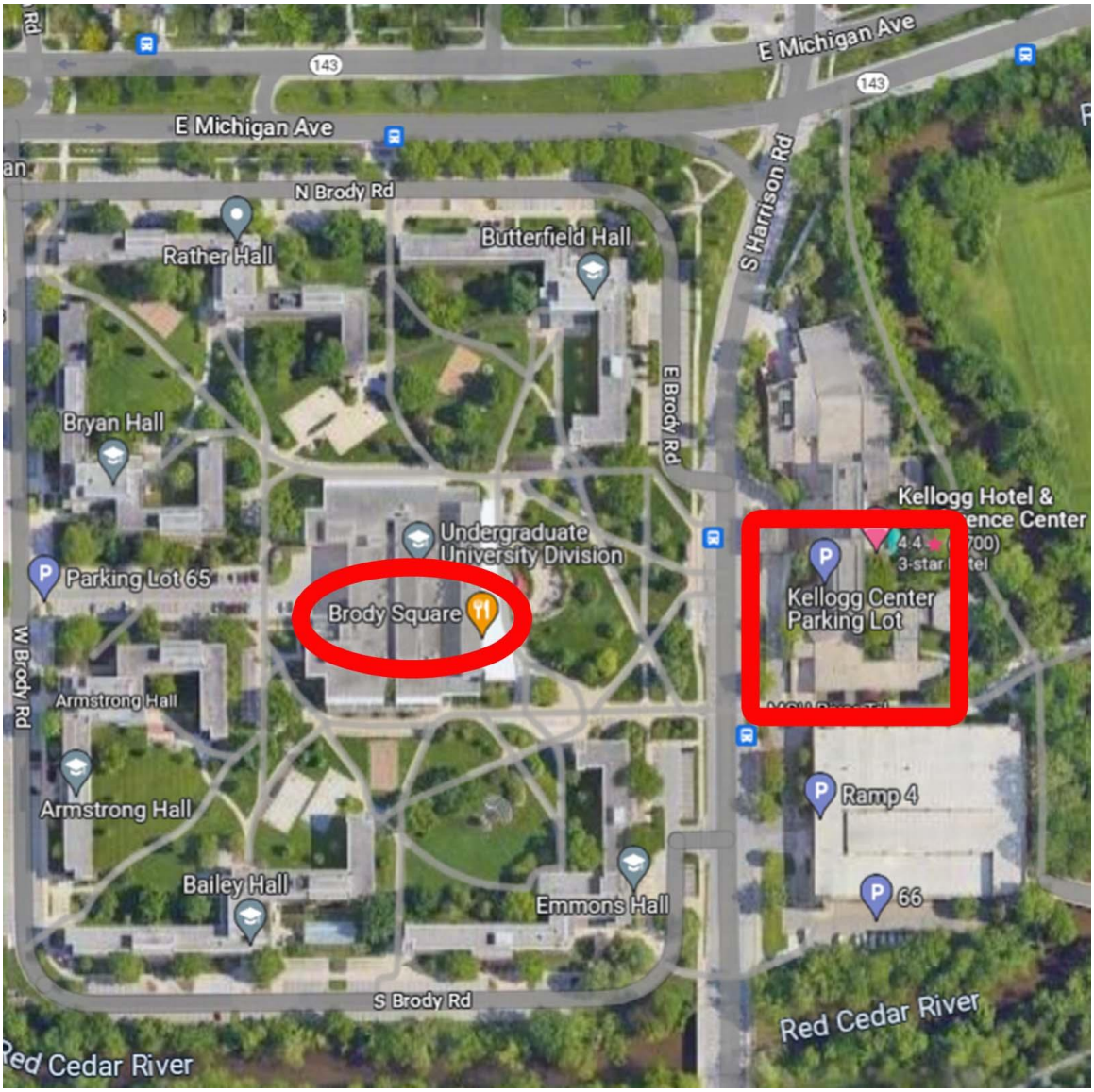
Acknowledgements

Michigan Chapter of SfN Council

	Name:	Institution:	Term Ends:
President	Anna Moszczynska	Wayne State University	2023*
Past President	Jessica Matchynski-Franks	Rochester University	2025
President-Elect			
Secretary	Harold Green	University of Detroit-Mercy	2023
Treasurer	Hilary Marusak	Wayne State University	2025
Awards Chair	Eric Ramsson	Grand Valley State University	2026
Website Coordinator	Bhairavi Srinageshwar	Central Michigan University	2023
Councilors:			
CMU	Julien Rossignol		2024
MSU	Joseph Patterson		2024
U of M	Sara Aton		2024
WSU	Kelly Bosse		2023
WMU	Lisa Baker		2023
Field Neuroscience Institute	Gary Dunbar		2024
At large I	Jessica Matyas	Rochester University	2023
At large II	Kevin Trewartha	Michigan Technological University	2024
Graduate student I	Candace Johnson	Western Michigan University	
Graduate student II	Lana Grasser	Wayne State University	2023

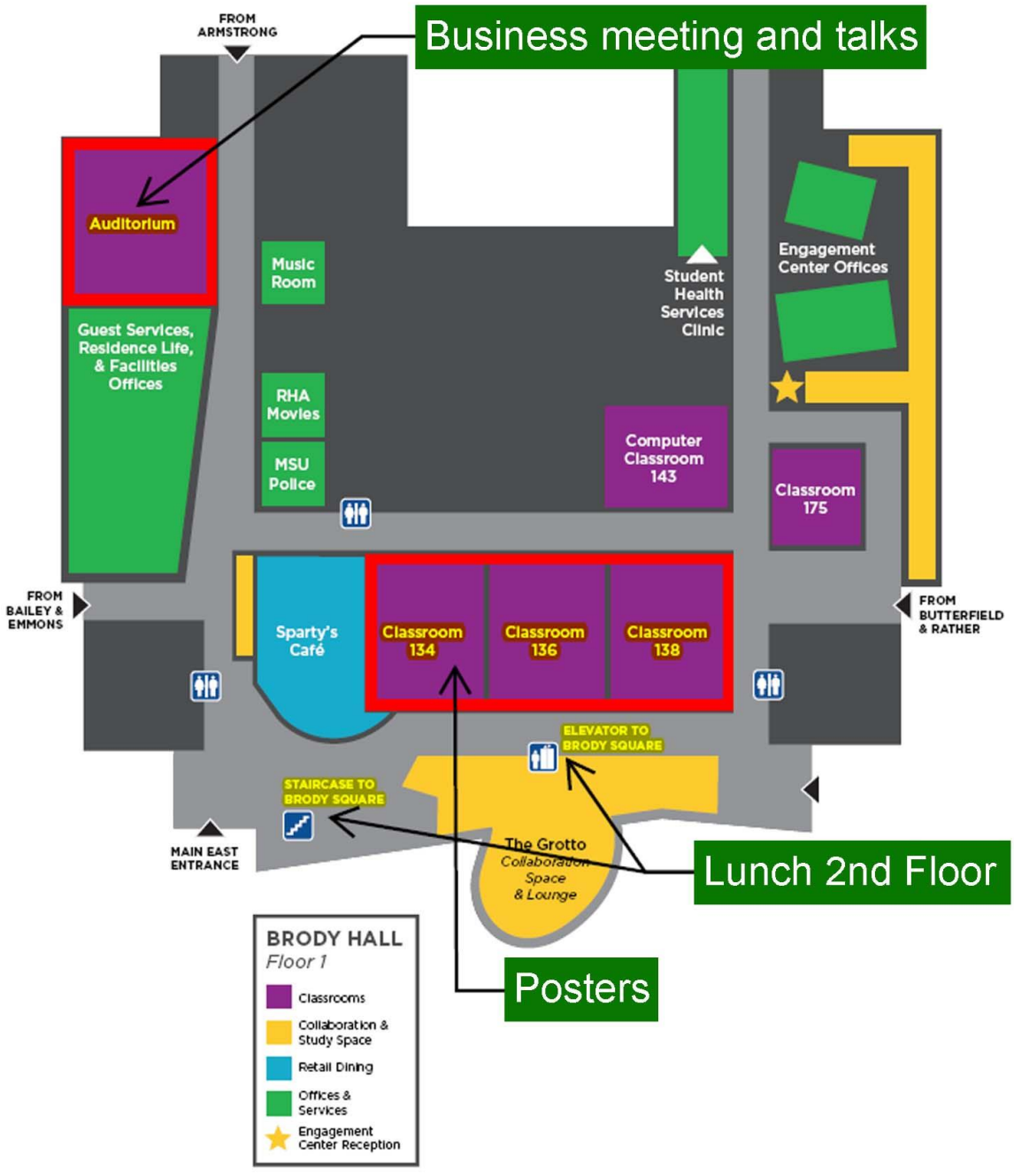
**Past President to retire & President-Elect to start tenure in 2023*

Brody Hall, 241 W. Broady Road, East Lansing, MI 48825



Parking is available at the Kellogg Center Parking Lot (Red Square). Brody Hall is located across the street (Red Circle)

Brody Hall Map



Founder's Awards

These awards are in honor of Montford F. Piercey and Duncan McCarthy for their contributions to organizing our chapter.

2023 Winner: Sierra Boyd

Department of Translational Neuroscience
Michigan State University

Developmental exposure to the Parkinson's disease-associated organochlorine pesticide dieldrin alters dopamine neurotransmission in the α-synuclein pre-formed fibril model

Biography

Sierra, a native Michigander from Muskegon, received her bachelor's degree in neuroscience from Michigan State University in 2019. During her undergraduate studies, she worked in preclinical research at Northern Biomedical Research and the Michigan State In Vivo Facility, where her research ranged from investigating the efficacy and delivery of gene therapy products to the central nervous system to testing snake venom antidotes. Sierra also worked in the Anantharam lab at the University of Michigan as a summer undergraduate research fellow studying synaptotagmin-mediated release kinetics in response to metabolic stress. In 2019, Sierra joined the pharmacology and toxicology PhD program with a dual major in environmental integrative toxicological sciences at Michigan State University in the labs of Alison Bernstein and Nick Kanaan in Grand Rapids.

Summary of work

Sierra's research focuses on how developmental exposures to neurotoxicants increase the risk of Parkinson's disease (PD). Specifically, she works on the Parkinson's disease-associated organochlorine pesticide, dieldrin. Developmental exposure to dieldrin is thought to induce a poised epigenetic state and to increase susceptibility to PD-related degenerative insults, possibly through alterations in dopamine packaging and neurotransmission. Utilizing a two-hit mouse model of Parkinsonian toxicity by combining developmental dieldrin exposure with the α-synuclein pre-formed fibril model, she is investigating alterations in dopamine signaling using fast-scan cyclic voltammetry and radioactive vesicular uptake assays. In addition to her *in vivo* work, Sierra is also executing a project using a 3D dopaminergic neurosphere model to screen genes with dieldrin-induced differential epigenetic marks and their role in susceptibility to PD-related toxicity.

Founder's Awards

These awards are in honor of Montford F. Piercey and Duncan McCarthy for their contributions to organizing our chapter.

2023 Winner: Carlye Szarowicz

Department of Translational Neuroscience
Michigan State University

Engaging the role of personalized medicine: impact of the rs6265 SNP in host and donor on dopamine neuron transplantation in Parkinson's Disease

Biography

Carlye received a B.S. in Biotechnology and in Forensic Biology from Ferris State University in December 2019. During her time at Ferris State, she had the opportunity to participate in several research projects including a pharmacokinetic study on a potential anti-cancer drug and the development of a MALDI-TOF mass spectrometry method for the detection of cannabinoid receptors in white blood cells. Notably, she also took part in an internship through Michigan State University at the Great Lakes Bioenergy Research Center in the Takahashi lab, working on metabolite profiling in switchgrass, a plant used as a bioenergy resource. In 2020, Carlye joined the Pharmacology and Toxicology graduate program at Michigan State University in the laboratory of Dr. Kathy Steece-Collier in Grand Rapids.

Summary of work

Carlye's research utilizes a CRISPR knock-in rat model of the human rs6265 brain derived neurotrophic factor (BDNF) single nucleotide polymorphism (SNP) to understand how this gene variant, which reduces available BDNF in the brain, impacts clinical responsiveness of individuals with Parkinson's disease (PD) to brain repair strategies. In previous neural grafting experiments conducted by the Steece-Collier lab, parkinsonian rats homozygous for rs6265 (aka: Met/Met) demonstrated paradoxical enhancement of neurite outgrowth and therapeutic efficacy despite a reduction of this important trophic factor compared to their wild-type counterparts. Advantages of rs6265 have also been observed in studies showing enhanced functional recovery in humans suffering from traumatic brain injury (TBI) and in a mouse stroke model. To expand understanding of the benefits as well as some distinct drawbacks of rs6265, Carlye is investigating the impact of this SNP when it occurs in either the host parkinsonian rats or in the nerve tissue donor in order to optimize brain cell grafting as a therapeutic option for PD. In addition, she is conducting *in vitro* experiments exploring novel functions of the Met BDNF pro-peptide, a portion of the larger BDNF protein, which she hypothesizes to play a role in neuroregeneration.

Keynote Speaker

The neurobiology of pain experience and its modulation by opioids

Gregory Scherrer, Ph.D.
Associate Professor
Department of Cell Biology and Physiology
University of North Carolina at Chappel Hill School of Medicine

Pain is a complex and multidimensional experience with sensory, affective and cognitive components. My lab aims to elucidate the mechanisms by which our nervous system generates the different dimensions of pain experience at the genetic, molecular, cellular, neural circuit, and behavioral levels, using the mouse as a model system. We also seek to resolve the mechanisms of action of opioids and understand how these drugs alter activity in neural circuits to produce analgesia, along with their deleterious side effects such as tolerance, addiction, and respiratory depression. To this aim, we develop and utilize cutting-edge techniques to investigate the functional organization of our endogenous opioid system and the cell-type specific localization, trafficking and signaling properties of opioid receptors in neurons in vivo. The ultimate goal of our research program is to use this novel knowledge to develop novel non-addictive analgesics and treatments for opioid use disorders to end the opioid epidemic.

Biography

Dr. Scherrer received his PharmD and PhD degrees from the University of Strasbourg, France. He subsequently completed two postdoctoral trainings, first in Neurophysiology of the Spinal Cord Dorsal Horn at University of California San Francisco and second in Neurobiology of Pain and its Control at Columbia University. Before moving to the UNC School of Medicine in Chapel Hill, he was an Assistant Professor at Stanford University.

Dr. Scherrer research current interests lie the neuroanatomy of neural circuits that underlie pain perception, opioid analgesia, and addiction. His laboratory investigates the sensory, emotional and cognitive dimensions of pain, and how opioids act in neural circuits to produce pain relief and their deleterious side effects such as tolerance, addiction and respiratory depression. Dr. Scherrer's multidisciplinary research combines molecular and cellular biology, neuroanatomy, electrophysiology, optogenetics, chemogenetics, in vivo recordings of neural activity, and behavioral experiments.

By uncovering the fundamental neurobiological processes by which our nervous system shapes pain experience and responds to opioids, Dr. Scherrer research aids the development of novel therapeutics to block pain more efficiently, and with reduced side effects, compared to current medications.

Dr. Scherrer mentors and trains graduate and undergraduate students as well as postdoctoral fellows. His research has been funded by multiple agencies, including the National Institutes of Health, Department of Defense, Rita Allen Foundation, McKnight Foundation, Brain Research Foundation, and the New York Stem Cell Foundation.

2023 Poster Assignments

Cognition

Session A

A1	Carmon H	VULNERABLE FOR ADDICTION-LIKE BEHAVIORS: DISRUPTED CHOLINERGIC SIGNALING AND EXAGGERATED (NEURO)IMMUNE RESPONSE IN SIGN-TRACKING RATS
A2	Carpenter C	ASSOCIATIONS AMONG SLEEP DURATION, ANXIETY SYMPTOMS, AND ACTIVITY OF FEAR NEUROCIRCUITRY IN YOUTH
A3	Ely SL	A SPOTLIGHT ON CHILDHOOD TRAUMA: PRELIMINARY FINDINGS LINKING TRAUMA AND POSTTRAUMATIC STRESS SYMPTOMS TO ALTERED ATTENTION-RELATED BRAIN AND BEHAVIOR IN YOUTH

Session B

B1	Tiscareno A	GENDER DIFFERENCES IN INTERHEMISPHERIC TRANSFER TIME IN MENTAL ROTATION TASK
B2	Moore M	THALAMO-CORTICAL DYNAMICS DURING A TEXTURE DISCRIMINATION TASK: PRELIMINARY RESULTS
B3	Cox H	IMPACT OF NEONATAL CANNABIDIOL (CBD) EXPOSURE ON THE REPRODUCTIVE SYSTEM OF ADULT MALE AND FEMALE RATS

Development

Session A

A4	Evanski J	WAKE UP AND SMELL THE COFFEE: ASSOCIATION BETWEEN MATERNAL CONSUMPTION AND WHITE MATTER MICROSTRUCTURE IN CHILDREN
A5	Hagan P	UTILIZING CRISPR-CAS9 TO GENERATE ZEBRAFISH MUTANTS FOR THE INTERLEUKIN-10 RECEPTOR
A6	Metiva J	EXAMINING MORPHOLOGICAL AND BEHAVIORAL EFFECTS OF PERINATAL PHTHALATE EXPOSURE IN LONG EVANS RAT
A7	Neagu A	EFFECT OF CANNABIDIOL AND NEONATAL PAIN EXPOSURE ON LONG-TERM COGNITIVE OUTCOME IN A RODENT MODEL

Session B

B4	Patel D	EFFECTS OF TRANSITIONING FROM MORPHINE TO BUPRENORPHINE (MEDICATION FOR OPIOID USE DISORDER) DURING PREGNANCY ON MATERNAL CARE AND OFFSPRING NEURODEVELOPMENT IN A TRANSLATIONAL RODENT MODEL

B5	Shemke A	THE ROLE OF NUCLEUS ACCUMBENS OXYTOCIN-EXPRESSING CELLS IN THE REGULATION OF JUVENILE SOCIAL PLAY
B6	Zundel C	CHILDHOOD AIR POLLUTION EXPOSURE IMPACTS DEVELOPMENTAL TRAJECTORIES OF CORE NEUROCOGNITIVE BRAIN NETWORKS

Integrative Physiology and Behavior

Session A

A8	Addy B	CORTICAL PRE-SACCADIC ACTIVITY FOR VERTICALLY-DIRECTED SACCADES
A9	Basarkod S	AMYGDALA REACTIVITY IS ASSOCIATED WITH WITH SKIN CONDUCTANCE RESPONSE IN PREDICTING FUTURE PTSD AND ANXIETY SYMPTOMS IN CHILDREN WITH TRAUMA EXPOSURE
A10	Beigloo F	SEX DIFFERENCES IN MONOAMINES TURNOVER AND BEHAVIORAL CORRELATES IN ZEBRAFISH: IMPLICATIONS FOR STUDYING INDIVIDUAL DIFFERENCES
A11	Burroughs RL	DIFFERENTIAL EFFECTS OF ENANTIOMERS OF THE NOVEL BENZOFURAN DERIVATIVE 1-(1-BENZOFURAN-5-YL)-2-(METHYLAMINO) PROPAN-1-ONE HYDROCHLORIDE (BK-5-MAPB) IN RATS TRAINED TO DISCRIMINATE STIMULANTS AND PSYCHEDELICS
A12	Caico S	ROLE OF VENTRAL TEGMENTAL AREA SGK1 PHOSPHORYLATION AND ACTIVITY IN DRUG-ASSOCIATED BEHAVIORS
A13	Jingwen, C	CONTROL OF EMOTION AND WAKEFULNESS BY NEUROTENSINERGIC NEURONS IN THE PARABRACHIAL NUCLEUS
A14	Gannot N	THE HETEROGENOUS FUNCTIONS OF THE NUCLEUS OF THE SOLITARY TRACT NEURONS IN BREATHING CONTROL
A15	Henry M	CHARACTERIZATION OF OXYTOCIN RECEPTOR BINDING DENSITY IN THE OXTR-ICRE RAT LINE TARGETING BRAIN REGIONS ASSOCIATED WITH SOCIAL BEHAVIOR
A16	Jiddou H	NOVEL BENZOFURAN AND BENZOTHIOPHENE ANALOGS ARE MONOAMINE RELEASING AGENTS THAT SUBSTITUTE FOR THE DISCRIMINATIVE STIMULUS EFFECTS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA)

Session B

B7	Khan R	NEUROTENSIN EXPRESSING LATERAL HYPOTHALAMIC NEURONS ALLEVIATE

		NEUROPATHIC AND INFLAMMATORY PAIN VIA NTS SIGNALING
B8	Orsucci I	TO PLAY OR NOT TO PLAY? UNDERSTANDING OPTIMAL CONDITIONS FOR STUDYING SOCIAL PLAY BEHAVIOR IN DIFFERENT LABORATORY RAT STRAINS
B9	Rajput N	IDENTIFYING NEURAL CORRELATES OF INDIVIDUAL DIFFERENCES IN ADULT ZEBRAFISH BEHAVIOR COMBINING IN-SITU HYBRIDIZATION CHAIN REACTION WITH ADULT ZEBRAFISH BRAIN ATLAS AND BRAINGLOBE
B10	Sapkowski K	ESTROGEN MEDIATES MELANIN CONCENTRATING HORMONE EXPRRESSING CELLS TO CONTROL TIME-DEPENDENT MOTIVATED FOOD SEEKING
B11	Schuh K	REGULATION OF STRESS AND ANXIETY IN A MOUSE MODEL OF HORMONAL CONTRACEPTIVES
B12	Steck K	DIETARY PROBIOTIC SUPPLEMENTS ATTENUATE RATE SUPPRESSANT EFFECTS OF MDMA IN MALE RATS TRAINED ON A DRL 18 REINFORCEMENT SCHEDULE
B13	Johnson A	EXAMINING THE BEHAVIORAL AND NEUROBIOLOGICAL CORRELATES OF BINGE EATING THROUGH AN ANALYSIS OF LICKING MICROSTRUCTURE AND C-FOS EXPRESSION
B14	Taylor D	THE NEURAL AND AUTONOMIC EFFECTS OF NON-INVASIVE VAGUS NERVE STIMULATION DURING ATTENTIONAL PROCESSES: AN EXAMINATION OF THE DOSE DURATION RESPONSE
B15	Valbrun SA	TRAUMA FROM THE EYE OF THE BEHOLDER
B16	Khalid S	INTERMITTENT MORPHINE ACCESS THROUGHOUT GESTATION IMPAIRS MOUSE MATERNAL BEHAVIOR DEVELOPMENT AND ENHANCES ANXIETY OUTCOMES

Motivation and Emotion

<u>Session A</u>

A17	Atasi T	UBIQUITIN-PROTEIN LIGASE PARKIN IN METHAMPHETAMINE USE DISORDER
A18	Caldwell A	ORGANIZATIONAL AND ACTIVATIONAL IMPACT OF OVARIAN HORMONES ON FEMALE RAT BINGE EATING BEHAVIOR
A19	Colon L	ROLE OF ENTORHINAL CORTEX NEURONS IN THE CONSOLIDATION AND/OR RECALL OF A COCAINE-CONTEXT MEMORY
A20	Fontana BD	USING MACHINE LEARNING TO IDENTIFY INDIVIDUAL DIFFERENCES IN FEAR RESPONSES AND MEMORY IN ZEBRAFISH (DANIO RERIO)

A21	Fex V	DISRUPTING COCAINE-SEEKING BY DEVALUING MEMORIES OF COCAINE REWARD THROUGH MESOLIMBIC CIRCUITRY
A22	Kalsi E	PAIRING OPTOGENETIC STIMULATION OF THE CENTRAL AMYGDALA WITH A CUE AMPLIFIES 'WANTING' MOTIVATION
A23	Kroll M	ROSTRAL AND CAUDAL VENTRAL PALLIDUM GABA NEURONS DIFFERENTIALLY CONTROL DISGUST AND AVERSION
A24	LeVasseur G	SINGLE PROLONGED STRESS OR NALOXONE-PRECIPITATED MORPHINE WITHDRAWAL AFFECTS CONDITIONED FEAR LEARNING USING FEAR-POTENTIATED STARTLE IN RATS BUT THEIR COMBINATION IS NOT ADDITIVE
A25	Liu W	THE INTERACTION OF EARLY LIFE STRESS AND HISTORY OF SWEET FLUID EXPOSURE ON MOTIVATION FOR ALCOHOL
A26	Mascarin AT	NEURONAL ENSEMBLES IN THE NUCLEUS ACCUMBENS CONTRIBUTE TO COCAINE-PRIMED SEEKING IN FEMALE AND MALE RATS

Session B

B17	Matsko M	BEHIND THE “RUNNER'S HIGH”: EFFECTS OF ACUTE EXERCISE, STRETCHING AND MEDITATION ON ANXIETY AND ENDOCANNABINOID LEVELS IN YOUTH
B18	Miller S	CENTRAL AMYGDALA CORTICOTROPIN RELEASING FACTOR NEURONS PROJECT TO THE VTA TO MEDIATE INCENTIVE MOTIVATION
B19	Ramaswami A	THE ROLE OF CENTRAL AMYGDALA CORTICOTROPIN RELEASING FACTOR NEURONS IN MOTIVATION AND ADDICTION
B20	Rivera QC	ROLE OF NEUROMEDIN S-EXPRESSING VENTRAL TEGMENTAL AREA NEURONS IN MORPHINE BEHAVIOR
B21	Sogbesan A	MEDIATIONAL PATHWAYS AMONG SUBSTANCE USE DURATION, CONSEQUENCES, AND QUIT ATTEMPTS
B22	Stemmler G	DISSOCIATING ‘LIKING’ AND ‘WANTING’ WITHIN THE VENTRAL PALLIDUM: AN OPTOGENETIC STUDY
B23	Sugimoto C	CHARACTERIZATION OF OXYTOCIN NEURONS AFFECTING SOCIAL BEHAVIORS
B24	Tittle L	THE ROLE OF NUCLEUS ACCUMBENS CORTICOTROPIN-RELEASING FACTOR IN INCENTIVE MOTIVATION
B25	Yahya M	CONSUMPTION OF OREO COOKIES DOES NOT LEAD TO BEHAVIORAL SENSITIZATION OR CHANGE FOS EXPRESSION IN THE NUCLEUS ACCUMBENS OF MALE AND FEMALE RATS
B26	Dodson O	INVESTIGATING THE ROLE OF GCG IN THE VENTRAL TEGEMENTAL AREA IN MORPHINE BEHAVIORS

B27	Gowatch L	ENDOCANNABINOIDS AND STRESS-RELATED DISORDERS: A SYSTEMATIC REVIEW OF BASAL LEVELS AND RESPONSES TO ACUTE PSYCHOSOCIAL STRESS

Neural Excitability, Synapses, and Glia

Session A

A27	Chavis G	THE SNX17-RETRIEVER ENDOMEMBRANE RECYCLING PATHWAY IS A KEY REGULATOR OF SYNAPTIC FUNCTION AND PLASTICITY IN HIPPOCAMPAL NEURONS
A28	Elvira CC	THE COORDINATION OF VOLTAGE-GATED SODIUM CHANNELS VIA ANKYRIN PROTEIN INTERACTIONS
A29	Stoll AC	THE PERSISTENT AND MULTIDIMENSIONAL MICROGLIAL RESPONSE TO PATHOLOGICAL ALPHA-SYNUCLEIN AGGREGATION

Session B

B28	Kolanowski MR	EFFECTS OF CANNABIDIOL ON COMPARTMENT SPECIFIC DOPAMINE RELEASE IN THE STRIATUM
B29	Zahoor I	MARESIN 1, A DOCOSAHEXAENOIC ACID-DERIVED PRO-RESOLUTION LIPID MEDIATOR, AMELIORATES INFLAMMATION, PROMOTES NEUROPROTECTION, AND PREVENTS DISEASE PROGRESSION IN PRECLINICAL ANIMAL MODEL OF MULTIPLE SCLEROSIS

Neurodegenerative Disorders, Sensory, and Motor Systems

Session A

A30	Atwa A	TAU INTERACTOME MAPPING USING THE BIOID2 APPROACH IDENTIFIES INTERACTIONS WITH PROTEINS ASSOCIATED WITH VARIOUS CELLULAR COMPARTMENTS
A31	Benskey MJ	SYNUCLEINOPATHY ACTIVATES THE COMPLEMENT SYSTEM AND DECREASES CD55 EXPRESSION IN NIGRAL NEURONS PRIOR TO NEURODEGENERATION
A32	Boyd SL	DEVELOPMENTAL EXPOSURE TO THE PARKINSON'S DISEASE-ASSOCIATED ORGANOCHLORINE PESTICIDE DIELDRIN INCREASES DOPAMINE RELEASE IN THE STRIATUM IN THE A-SYNUCLEIN PRE-FORMED FIBRIL MOUSE MODEL

A33	Dajai C	THE CREATION OF A NOVEL TRANSGENIC FLY LINE TO MODULATE TAU PHOSPHORYLATION NEAR THE CALPAIN CLEAVAGE SITE
A34	Combs B	PATHOGENIC TAU MUTANTS ACTIVATE P38 MAPK AND DISRUPT FAST AXONAL TRANSPORT
A35	Garapati S	CHEMOTAXIS OF PARENCHYMAL MICROGLIA FOLLOWING THE DEATH OF INNER RETINAL NEURONS INDUCED BY INTRAVITREAL INJECTION OF NMDA IN ZEBRAFISH
A36	Hampton C	THE EFFECT OF SUBSTRATE STIFFNESS ON HUMAN SCHWANN CELL ELONGATION, MIGRATION, AND PROLIFERATION
A37	Howe J	IDENTIFICATION OF THE EARLY MICROGLIA TRANSCRIPTOMIC RESPONSE TO ALPHA-SYNUCLEIN INCLUSION FORMATION IN THE SUBSTANTIA NIGRA FOLLOWING PREFORMED FIBRIL INJECTION
A38	Ikefuama E	TARGETED CIRCUIT MANIPULATION FOR AMELIORATING HUNTINGTON'S DISEASE PATHOGENESIS
A39	Keene J	INFLAMMATORY STRESS CONTRIBUTES TO TAU PATHOLOGY IN THE PS19 MOUSE MODEL OF ALZHEIMER'S DISEASE
A40	King M	USE OF SURFACE MODIFIED GENERATION 4 PAMAM DENDRIMER NANOMOLECULES TO DELIVER NEUROPROTECTIVE HORMONE, PROGESTERONE TO ISCHEMIC STROKE INDUCED RATS
A41	Kubik M	DISEASE MODIFYING POTENTIAL OF THIRD GENERATION ROCK INHIBITOR KL-00974 IN SYNUCLEINOPATHY MODELS OF PARKINSON’S DISEASE
A42	Malewicz J	UNIQUE OXIDATIVE STRESS SIGNATURES IN PAIN AND REWARD BRAIN REGIONS AFTER TBI IN MALE AND FEMALE MICE
A43	Poudel A	CURCUMIN PREVENTS THE DEVELOPMENT OF MOTOR DEFICITS IN GFAP-IL 6 MOUSE MODEL WHEN DELIVERED USING MIXED-SURFACE G4 PAMAM DENDRIMERS

Session B

B30	Sundararaghavan H	EFFECT OF ELECTRICAL STIMULATION ON PLEXIFORM NEUROFIBROMA SCHWANN CELLS
B31	Szarowicz C	ENGAGING THE ROLE OF PERSONALIZED MEDICINE: IMPACT OF THE RS6265 SNP IN HOST AND DONOR ON DOPAMINE NEURON TRANSPLANATION IN PARKINSON'S DISEASE
B32	Taylor K	DEVELOPING AND IMPROVING A BIOLUMINESCENT GABA SENSOR
B33	Zunnu RA	ELECTRICAL STIMULATION OF DUAL-LAYER MICROSPHERES FOR CONTROLLED DRUG DELIVERY FOR NERVE REGENERATION

B34	DuBois KN	ASSESSING A CLINICAL COHORT USING A PLASMA ALZHEIMER'S DISEASE BIOMARKER PANEL
B35	Hore M	DEVELOPMENT OF A NOVEL TRANSLATIONAL RAT MODEL OF DEMENTIA WITH LEWY BODIES
B36	Kara B	WHERE DO PATHOLOGY AND COGNITIVE DECLINE MEET IN ALZHEIMER'S DISEASE?
B37	Soliman A	EFHD2 TRANSFORMS MONOMERIC AND FILAMENTOUS TAU INTO TANGLE-LIKE STRUCTURES IN VITRO
B38	Azzo C	SENSORY PROCESSING AND BEHAVIORS OF CHILDREN: RETROSPECTIVE ANALYSIS OF CLINICAL DATA
B39	Ebendick B	IMUNNE MODULATION EFFECTS ON NEUROPLASTICITY IN ZEBRAFISH
B40	Spoelman A	A STRUCTURAL DISSECTION OF SENSORY INNERVATION WITHIN THE MOUSE AIRWAY
B41	Kim HH	IDENTIFICATION OF AN INHIBITORY CIRCUIT THAT MEDIATES MOTOR INTEGRATION IN THE SOMATOSENSORY CORTEX
B42	White B	ACETYLCHOLINESTERASE REACTIVATION AMELIORATES CHLORPYRIPHOS MEDIATED DOPAMINERGIC CELL LOSS
B43	Sim J	PERIPHERAL INTERLEUKIN-10 CONTRIBUTES TO SEX DIFFERENCES IN PAIN RESOLUTION
B44	de Souza S	MAST CELLS ARE NECESSARY FOR THE RESOLUTION OF PAIN HYPERSENSITIVITY AFTER SKIN INJURY

Techniques

Session A

A44	Almaat A	EXTRACTING NEUROIMAGING QUALITY METRICS USING MRIQC
A45	Silvagnoli A	ACTIVITY IMAGING AT DEPTH WITH BIOLUMINESCENCE
A46	Simkins J	A NOVEL METHOD FOR MOLECULAR EVOLUTION OF BL-OG COMPONENTS UTILIZING PHOTO-SENSITIVE TRANSCRIPTION FACTOR EL222

Session B

B45	Slaviero A	IMPROVED BIOLUMINESCENT-OPTOGENETIC TOOLS FOR MANIPULATION OF NEURAL CIRCUITS
B46	Srinageshwar B	DELIVERY OF NOCODAZOLE USING PAMAM DENDRIMER NANOMOLECULES TO IMPROVE SURVIVABILITY OF SCID MICE WITH HUMAN GLIOBLASTOMA
B47	Tamimi R	MINIMIZING ARTIFACT WITH MULTI-ECHO FMRI DATA ACQUISITION AND PREPROCESSING: AN EXAMPLE IN A STUDY OF CHILDREN AND ADOLESCENTS

History and Education

Session A

A47	Hagenauer M	THE BRAIN DATA ALCHEMY PROJECT: TEACHING RESEARCH REPRODUCIBILITY AND DISCOVERY SCIENCE WHILE MINING GOLD FROM ARCHIVED GENOMICS DATA

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Abstracts

A1

VULNERABLE FOR ADDICTION-LIKE BEHAVIORS: DISRUPTED CHOLINERGIC SIGNALING AND EXAGGERATED (NEURO)IMMUNE RESPONSE IN SIGN-TRACKING RATS

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Certain cues in an environment can gain motivational properties when directly associated with a reward. In turn, the cue can prompt individuals to engage in certain reward-driven behaviors eventually manifesting into addiction. The Pavlovian Conditioned Approach (PCA) task allows researchers to study the extent to which cues in the environment, or the conditioned stimuli, control behavior based on the conditioned response that develops. When rats are screened through the Pavlovian Conditioned approach procedure, two phenotypes emerge: sign-trackers and goal-trackers. Sign-tracking (ST) rats are prone to attribute incentive salience toward reward cues, which can manifest as a propensity to approach and contact Pavlovian cues. STs also exhibit poor attentional performance, relative to their counterparts, the goal-trackers (GTs). The attentional control deficits that are seen in STs have previously been attributed to the failure to translocate intracellular choline transporters (CHTs) into the synaptosomal plasma membrane, thereby failing to support choline import, acetylcholine synthesis, and release. Here we investigated post-translational modifications – poly-ubiquitination -- responsible for disrupted CHT trafficking in STs, with the hypothesis that attenuated cholinergic activity in STs causes an exaggerated (neuro)immune response. Intracellular CHTs, but not plasma membrane CHTs, were highly ubiquitinated in STs when compared with GTs. Activation of the innate immune system by systemic administration of the bacterial endotoxin lipopolysaccharide (LPS) caused ubiquitinylation levels of CHTs from the cortex and striatum to drastically increase in GTs, but not STs. This suggests that in unchallenged STs, ubiquitinylated CHTs are already at maximum levels and unresponsive to an additional immune challenge, leading to a potential ceiling effect in STs. We further investigated the role of immune modulators, cytokines, in CHT ubiquitination. Cytokine levels measured in the frontal cortex and striatum, but not the spleen, were higher in STs than in GTs prior to an immune challenge. Administration of LPS increased levels of most cytokines in both phenotypes in the spleen. In the cortex and striatum, LPS particularly increased levels of the chemokines, CCL2 and CXCL10, in both STs and GTs; however, all other phenotype-specific increases in cytokine levels following LPS administration were restricted to GTs only. This again suggests a potential ceiling effect in STs. Therefore, the interaction between elevated brain immune modulator signaling and CHT regulation are essential components of the neuronal underpinnings of the addiction vulnerability trait indexed by sign-tracking.

A2

ASSOCIATIONS AMONG SLEEP DURATION, ANXIETY SYMPTOMS, AND ACTIVITY OF FEAR NEUROCIRCUITRY IN YOUTH

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Background: The transition from childhood to adolescence are marked by a reduction in sleep duration and increase in risk of anxiety and other common psychiatric disorders. Prior functional magnetic resonance imaging (fMRI) studies in adults suggest that poor sleep is associated with altered activation of fear neurocircuitry, including the amygdala and ventromedial prefrontal cortex (vmPFC)—which may explain the close bidirectional relationship between poor sleep and anxiety risk. However, these associations have not yet been explored during childhood or adolescence. In the present study, we tested whether shorter typical sleep duration is associated with (1) greater anxiety symptoms, (2) poorer extinction recall—a measure of fear dysregulation, and (3) altered activation of amygdala-vmPFC fear neurocircuitry in youth.

Methods: Ninety-four youth (49 female, ages 6-17) completed a two-day fear extinction and recall paradigm during fMRI scanning. Typical sleep duration on school and free (i.e., weekend, non-school) days, as well as between the two visits, was measured using self-report. Activity in fear neurocircuitry, as well as measures of conditioned fear (i.e., skin conductance responses, unconditioned stimulus expectancy ratings) were measured on day 2. Anxiety symptoms were measured using self-report.

Results: Shorter typical sleep duration on school days was significantly associated with greater anxiety symptoms when controlling for age and sex (β=-3.332, p=0.020). Sleep duration on free days, or between visits 1 and 2, was not associated with anxiety. Sleep variables were not associated with measures of conditioned fear. However, shorter sleep duration between visits 1 and 2 was associated with lower activation in the vmPFC, and greater activation in the cerebellum, visual cortex, and dorsomedial prefrontal cortex ($p<0.001$, 10 voxel minimum).

Discussion: Shorter typical sleep duration on school days was associated with greater anxiety symptoms, and shorter sleep the night before the scan was associated with alterations in fear neurocircuitry in youth. In particular, youth who slept for fewer hours the night before the scan showed lower activity in the vmPFC, which is associated with the regulation of fear, and greater activity in brain regions associated with the expression of fear (e.g., dorsomedial prefrontal cortex). Future studies should examine whether alterations in fear neurocircuitry explain the previously reported link between poor sleep and the emergence of anxiety in youth.

A3

A SPOTLIGHT ON CHILDHOOD TRAUMA: PRELIMINARY FINDINGS LINKING TRAUMA AND POSTTRAUMATIC STRESS SYMPTOMS TO ALTERED ATTENTION-RELATED BRAIN AND BEHAVIOR IN YOUTH

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Background: More than two-thirds of children experience a traumatic event (e.g., violence, sexual abuse) before reaching adulthood. Exposure to childhood traumatic events (CTEs) can lead to an increased risk for developing posttraumatic stress symptoms (PTSS) and unwanted psychological effects such as emotional arousal and altered cognition (e.g., attention). Emerging research has examined the impact of trauma and PTSD on attention-related brain functioning in adult populations. However, little remains known about the impact of CTEs and PTSS on attention-related brain and behavioral functioning during adolescence, a period of substantial neurodevelopment and elevated psychiatric risk. Here, we report on preliminary data from an ongoing study that aims to explore these associations in a sample of youth with a high incidence of trauma exposure.

Methods: To date, 33 Detroit-area adolescents (63.6% male, M±SD=13.2±2.2 years) have participated in the study. While undergoing functional neuroimaging, participants completed a modified, child-friendly version of the Attention Network Test, which assesses performance of the alerting, orienting, and executive attention networks. Information about adolescents' CTEs and PTSS were queried through the University of California-Los Angeles Posttraumatic Stress Disorder Reactivity Index and served as predictors for attention-related behavior (measured via reaction time) and brain activation ($p \geq 0.005$, cluster size minimum=10 voxels).

Results: The majority of youth (90.9%) endorsed experiencing at least one traumatic event (M±SD=3.6±2.7 traumatic events), though PTSS remained lower and variable for the sample (M±SD=16.7±14.2). Behaviorally, only PTSS and orienting attention performance showed a significant relationship, indicating greater PTSS were associated with slower orienting attention. Interestingly, during orienting attention portions of the task, CTEs and PTSS were associated with higher activation in the left superior frontal gyrus and fusiform gyrus, respectively. With regard to alerting attention, CTEs were associated with lower activation in the left/right superior and right middle frontal gyri, whereas PTSS were associated with lower activation in the left inferior parietal lobe. During executive attention, CTEs and PTSS demonstrated similar effects on the brain, showing lower activation in the precuneus, left/right inferior parietal lobe, supramarginal, and angular gyri. PTSS were additionally related to lower activation in both hemispheres of the frontal cortex, including the medial, superior, and inferior gyri and anterior cingulate.

Conclusion: CTEs and PTSS had differential effects on attention-related brain functioning. In particular, areas involved in spatial orienting demonstrated higher activation while areas involved in executive control of attention showed lower activation. Though preliminary, this data implies that trauma exposure and subsequent symptoms may impact attention-related processes during adolescence. Future work should examine this relationship further and explore if and how the development of these processes is affected by trauma exposure.

B1

GENDER DIFFERENCES IN INTERHEMISPHERIC TRANSFER TIME IN MENTAL ROTATION TASK

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Past neuropsychology studies on interhemispheric transfer times (IHTT) have shown faster transfer from the right hemisphere to the left hemisphere than in the other direction when performing a language-related task (Moes et al., 2007; Brown et al.,1994). In addition, females had faster and more symmetric transfer times overall. The current study sought to examine the impact on IHTT when participants perform a right hemisphere dominant task. We predicted that new task would result in faster left-to-right IHTT for males, but symmetric IHTT for females. Participants performed a mental rotation task using mirrored and non-mirrored letters. Continuous EEG recordings were segmented, and the N170 latency ERP wave was used to index the IHTT in each direction. Experiment 1 produced results partially consistent with the hypothesis. Experiment 2 modified the task to increase the right-hemisphere dominance. A three-way repeated-measures ANOVA for gender, direction of transfer, and experiment was conducted. The three-way interaction was significant with Experiment 2 producing faster left-to-right IHTT than Experiment 1, and females showing more symmetrical IHTT, and overall faster transfer time than males. Taken together the results suggest that the nature of the task as well as the specialization of each hemisphere impact IHTT results.

Keywords: Gender difference, Interhemispheric Transfer Time, Mental rotation

B2

THALAMO-CORTICAL DYNAMICS DURING A TEXTURE DISCRIMINATION TASK: PRELIMINARY RESULTS

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We study combined neural recordings and behavioral videos from mice trained on a texture discrimination task. The neural recordings consist of a single hemisphere of wide field calcium imaging combined with an array of 32 optical fibers inserted into thalamic nuclei and the amygdala. Behavior is monitored by a body-camera and a second camera recording whisking and licking. Our preliminary dataset consists of 15 roughly one-hour sessions with 3 trained mice. We have developed a pre-processing pipeline that includes motion correction, alignment, and normalization of the calcium data, together with Deeplabcut processing and alignment of the behavioral videos. Our goals are to combine these recordings with anatomical connectome data and study the network dynamics of the thalamocortical circuits. In particular, we aim to study trial-to-trial variations in network dynamics and how these can be related to trial outcomes, initial brain states, and the spontaneous behaviors of the animals. In preprocessing we find large (~15 micron) rigid motions which correlate with body movements. In a preliminary analysis of network dynamics, we see a decrease in correlations between auditory, motor, and parietal association areas with respect to the other cortical and thalamic regions, during “hit” trials where the animal actively seeks a reward. Strong changes in network dynamics are observed during licking (water reward) behavior. Attentive task-oriented behavior is accompanied by an increase in correlation between cortical motor areas and a subset of thalamic nuclei.

B3

IMPACT OF NEONATAL CANNABIDIOL (CBD) EXPOSURE ON THE REPRODUCTIVE SYSTEM OF ADULT MALE AND FEMALE RATS

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A significant proportion of humans are born preterm today, and preterm infants undergo numerous painful procedures while they are in the Neonatal Intensive Care Unit (NICU) such as, blood draws, injections, intubation etc. There are currently no effective pharmacological pain management strategies for reducing the pain from these standard procedures, but cannabidiol (CBD) has been suggested as a potential safe candidate for pain management in neonates. However, previous preclinical research has suggested that CBD may have effects on the reproductive system of those exposed. The aim of this study was to investigate the effect CBD on the neurodevelopment of neonatal rats with a particular focus on their reproductive system. The study involved assigning the rat pups into one of six groups (experimental/pain: 0mg/mL, 5mg/mL, 10 mg/mL CBD groups & Control/touch: 0mg/mL, 5mg/mL, 10 mg/mL). The pain groups were pricked by a needle on their paws 4 times a day from postnatal days (PND) 2-5, while the controls' paws were touched with a brush. Once the offspring reached adulthood both groups were put through a series of behavioral tests (i.e. hot plate test (nociception), restraint tests (stress response), elevated zero maze (anxiety-like behavior), etc.), before being perfused to collect brains and reproductive organs (testes, ovaries). We measured the weight of the testis (males) and will weigh ovaries (females) as well as slice the epididymis to perform a sperm count or qualitative analysis. Further, blood samples were collected at the time of sacrifice to measure testosterone (males) and estrogen levels (females) in all groups using enzyme-linked immunoassays (ELISA). Preliminary results suggests that neither CBD or neonatal pain exposure has an impact on adult testes' weights. However, we hypothesize that the rats that were exposed to CBD as pups may have a lower sperm quality and testosterone levels in comparison to the controls, with no impact on the female gonadal weights or estrogen levels. More research is needed to evaluate whether CBD may have protective effects after neonatal pain exposure and whether it is safe for the development of the reproductive system.

A4

WAKE UP AND SMELL THE COFFEE: ASSOCIATION BETWEEN MATERNAL CONSUMPTION AND WHITE MATTER MICROSTRUCTURE IN CHILDREN

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Caffeine is frequently consumed by pregnant individuals. Research has shown that prenatal caffeine exposure (PCE) negatively impacts offspring development by inhibiting fetal growth and increasing risk of premature birth and externalizing symptoms in childhood. Furthermore, PCE may alter neurodevelopment, including the development of frontolimbic pathways associated with cognitive and emotion-related functioning. We investigated the relationship between PCE and fractional anisotropy (FA) of frontolimbic white matter microstructure during childhood (M±SD age=9.92±0.62 years; 47.8% female) using data from the ABCD Study (n=6,375), estimating caffeine intake using parent retrospective report. FA was estimated for white matter tracts (five/hemisphere) from DTI data. PCE was split into groups: 1) no PCE, 2) <2 cups caffeine/day- “recommended dose”, 3) >3 cups caffeine/day- “high dose”. No PCE was reported in 64.3% of the sample, 31% consumed the recommended dose, and 4.7% consumed the high dose. When controlling for relevant covariates and multiple comparisons correction, results indicated that compared to unexposed children, high dose children had lower FA in eight of the ten tested tracts, including: the right fornix, left fornix, right cingulum bundle, right parahippocampal cingulum, right inferior fronto-occipital fasciculus, left inferior fronto-occipital fasciculus, right uncinate, and left uncinate. When comparing the recommended dose and high dose groups, children in the high dose group had lower FA of the right fornix (β=-0.00567, p=0.002), left inferior fronto-occipital fasciculus (β=-0.00413, p=0.023), right uncinate. (β=-0.00406, p=0.03), and left uncinate (β=-0.00485, p=0.014). After multiple comparisons correction, the right fornix was the only tract that remained significant (pFDR>0.05). These results add to the literature indicating PCE may negatively impact offspring neurodevelopment.

A5

UTILIZING CRISPR-CAS9 TO GENERATE ZEBRAFISH MUTANTS FOR THE INTERLEUKIN-10 RECEPTOR

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Zebrafish possess the innate ability to regenerate a variety of damaged tissues, including the heart, fins and central nervous system. In the retina, experimental photoreceptor cell death ultimately results in photoreceptor regeneration and restoration of visual function. The regeneration of photoreceptors involves reprogramming of Müller glia and proliferation of Müller glia-derived progenitors, which differentiate into photoreceptor cells. In zebrafish, inflammation is required to effectively trigger the regenerative process. However, unresolved inflammation causes the death of regenerated photoreceptor cells. One component of inflammation is Interleukin-10 (Il-10), an anti-inflammatory cytokine that serves to downregulate the expression of pro-inflammatory genes. In Il-10 loss of function mutants, pro-inflammatory components are elevated, and photoreceptor death results in hyperproliferation of Müller glia-derived progenitors and compromised regeneration of photoreceptors.

To better understand the mechanisms underlying Il-10 function during photoreceptor regeneration, we undertook experiments to create loss of function mutants for the Il-10 receptors, Il-10ra and Il-10rb. Utilizing genome editing via CRISPR-Cas9, we designed three gRNAs to target three separate exons of each gene. Single-cell stage embryos are injected with gRNAs against il10ra or il10rb along with Cas9 protein. Genomic DNA of F0 embryos was extracted from both injected and un-injected siblings at 4 days post fertilization and analyzed by PCR using primers that span the three targeted exons. Genomic DNA from uninjected siblings amplified a single band of 1.4 kbp in predicted size. About 70% of il10ra gRNAs injected embryos produced smaller bands in size. Of these injected embryos, 44% showed a lack of band in predicted size, suggesting complete disruption of the wildtype allele. To further confirm CRISPR-mediated mutations, amplified bands were processed for Sanger sequencing. We found that large deletions corresponded to on-target genomic regions of il10ra. The overwhelming outcome was a large frameshift mutation resulting in premature stop codons and predicted truncations of the protein. Similar results were observed in embryos injected with il-10rb gRNAs. These results indicate successful mutations and predicted interruptions of Il-10ra and Il-10rb in F0 animals. Assays on inflammation, proliferation of Müller glia-derived progenitors, and photoreceptor regeneration in these F0 mutants are underway.

A6

EXAMINING MORPHOLOGICAL AND BEHAVIORAL EFFECTS OF PERINATAL PHTHALATE EXPOSURE IN LONG EVANS RAT

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In classic work by William C. Young's research laboratory, it was established that the organization of mammalian brain morphology is guided by gonadally expressed hormones in utero. This means that while the genetic sex of an organism may typically drive phenotypic development of sexual morphology and the brain, the environment also exerts a significant effect. Phthalates are esters of the chemical phthalic acid and are used as plasticizing agents to increase the flexibility and transparency of plastics, especially polyvinyl chloride. Due to their widespread prevalence in plastics associated with daily life, nearly all individuals tested display metabolites of phthalates in expressed urine. A growing body of evidence suggests that phthalates disrupt hormone function and activity in the body of animals. Impact has been identified in sexual behavior, anogenital distance, fertility, and some components of neurobehavioral development. We theorize that perinatal exposure to phthalates may influence development by reshaping the organization of the mammalian central nervous system in ways to allow phenotypic expression of morphology and behavior. In this research, we examine the effects of perinatal phthalate exposure compared to control in populations of the Long-Evans rat in the juvenile and post-pubescent stages of development.

A7

EFFECT OF CANNABIDIOL AND NEONATAL PAIN EXPOSURE ON LONG-TERM COGNITIVE OUTCOME IN A RODENT MODEL

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Infants born preterm face several health concerns such as breathing problems, heart problems, or temperature control issues. To combat these and other complications, preterm infants are kept in neonatal intensive care units (NICUs) where they receive intensive care during their first weeks of life. However, this care often involves receiving many painful procedures per day due to necessary injections, intubations or blood draws, and most of these procedures are performed without the use of adequate pain management. Repeated pain exposure in the neonatal period, is known to have detrimental effects on neurodevelopment, especially in very preterm infants (i.e. under 32 weeks gestational age). Specifically, repeated pain exposure during this time, can lead to slower brain maturation as well as adverse cognitive outcomes. Additionally, previous preclinical studies have demonstrated that repeated neonatal procedural pain exposure alters learning and memory in adult rats. The endocannabinoid system has been suggested as a novel target for pain management. Therefore, this study aimed to investigate if neonatal pretreatment with the cannabinoid cannabidiol (CBD) could prevent neonatal procedural pain from altering learning and memory in adult rats, as assessed via the Novel Object Recognition (NOR) test. We hypothesized that rats exposed to procedural pain would display impaired memory in the NOR test compared to touch control subjects. Further, we expected this effect to be mitigated in subjects who received CBD before repeated pain exposure. However, our preliminary results revealed some interesting interaction effects of sex, pain, and CBD, with the high-dose CBD group that was also exposed to pain spending more time investigating the novel object, but we did not see an overall impairment in the pain group compared to controls unfortunately. This elucidates that more exploration is necessary to better understand the impact of neonatal pain and the potential for protective effects of CBD on long-term cognitive outcomes as new and effective methods of pain management for preterm infants are desperately needed.

B4

EFFECTS OF TRANSITIONING FROM MORPHINE TO BUPRENORPHINE (MEDICATION FOR OPIOID USE DISORDER) DURING PREGNANCY ON MATERNAL CARE AND OFFSPRING NEURODEVELOPMENT IN A TRANSLATIONAL RODENT MODEL.

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In 2020, 2.7 million people have been diagnosed with Opioid Use Disorder (OUD). Of particular concern, there has been a dramatic increase in opioid misuse among pregnant women with the number of OUD diagnoses during pregnancy increasing by a factor of four from 1999 to 2014. Pregnant women who are diagnosed with OUD are often prescribed medications for opioid use disorder (MOUD) such as buprenorphine (BUP). BUP is a semi-synthetic partial mu-opioid agonist and kappa-opioid antagonist which has since replaced methadone as the gold standard for OUD treatment. Evidence suggests that MOUD treatment (i.e., BUP) results in better outcomes for exposed infants as compared to discontinuation of illicit opioids or the continuous use of illicit opioids during pregnancy. In the current study, we are utilizing a translational rodent model to investigate the effects on maternal care and offspring neurodevelopment outcomes after the transition from morphine to buprenorphine during pregnancy. Adult female rats were randomly assigned to one of five experimental groups; Control- vehicle (V), BUP continuous (BC), morphine continuous (MC), morphine to BUP (MB), or morphine to vehicle (MV). We started to administer drugs 7 days prior to breeding, to ensure drug dependence. The MB group received morphine until gestational day 4 (GD4) and then switched to BUP until postnatal day 2 (PN2). The MV group was switched to saline after GD4. The BC and MC groups received BUP or morphine continuously until PN2. These experimental groups are meant to simulate real-world scenarios in which pregnant women are either already taking BUP (BC), are switched to BUP once they become aware of their pregnancy (MB), try to stop taking the illicit drug (MV), or continue using an illicit opioid (MC). Dams' maternal care behaviors, pup retrieval, and hot plate tests were observed, and measurements of offspring mortality and neurodevelopment (weight, length, surface righting, and Neonatal Withdrawal Syndrome (NOWS)) were taken. On PN2, dams and pups were sacrificed, and their blood and brains were collected for further analysis. Preliminary results suggest that there is a deficit in maternal care behaviors within the BC and MB groups (Nesting initiation, most deceased pups, and the least number of milk bands seen in pups). Further, we observed decreased maternal motivation (pup retrieval) in the BC group and NOWS symptoms in MC, BC, and MB pups. Interestingly, 3 out of 10 MB dams seem to have lost their pregnancies after the switch to BUP on GD 5. However, the final data analysis is still in progress. Our findings will shed light on how different opioids affect neurodevelopmental outcomes of the offspring and maternal care behavior and whether shifting from morphine to BUP may prevent negative effects compared to chronic morphine administration.

B5

THE ROLE OF NUCLEUS ACCUMBENS OXYTOCIN-EXPRESSING CELLS IN THE REGULATION OF JUVENILE SOCIAL PLAY

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Juvenile social play, also known as rough-and-tumble play, is an important and rewarding behavior displayed in many animal species, including humans and rats. Social play is known to contribute to social competency in adults. Children with autism spectrum disorder (ASD) show deficits in social play, which can cause difficulty navigating later social situations as evidenced by higher rates of social anxiety and depression. Thus, understanding how the brain regulates social play could inform potential therapeutics for social deficits associated with ASD.

Oxytocin (OXT) has shown to regulate various social behaviors, however, its role in juvenile social play is relatively understudied. The nucleus accumbens (NAc), a brain region associated with reward and motivation, has a dense population of neurons expressing OXT receptors (OXTR). Preliminary findings from our lab indicate that blocking OXTRs in the NAc alters social play at sex-specific doses, but the necessity of NAc-OXTR neuronal activity during social play is unknown.

To explore this, we used a technique called Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). DREADDs target specific cells by inserting a “designer receptor” which is only activated by binding of the “designer drug”, Clozapine-N-Oxide (CNO). In this way, we were able to inhibit the activity of OXTR-expressing neurons in the NAc to study how changes in NAc-OXTR activity alter the expression of social play, and if this occurs sex-specifically. We found that while social play behavior was not altered, social investigation showed a trend towards an increase in females. Due to the limited number of subjects, more cohorts must be tested to confirm these findings. This information could be used in the future to better design sex-specific treatments for ASD.

B6

CHILDHOOD AIR POLLUTION EXPOSURE IMPACTS DEVELOPMENTAL TRAJECTORIES OF CORE NEUROCOGNITIVE BRAIN NETWORKS

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Air pollution exposure has been associated with adverse mental health outcomes. Youth may be particularly susceptible given ongoing brain development. However, the neurobiological mechanisms underlying the association between air pollution and mental health remain unclear. We examine the impact of air pollution, specifically, fine particulate matter (PM2.5), on resting-state functional connectivity (rsFC) of the salience network, a network involved in attentional orienting to emotional and sensory stimuli, during the transition into adolescence.

The sample consisted of baseline and two-year follow-up data from 4,911 youth in the Adolescent Brain Cognitive Development Study (M+SD=9.92+0.62 years; 45% female). One-year annual ambient PM2.5 concentrations during late-childhood were estimated using hybrid ensemble spatiotemporal modeling. The Child Behavioral Checklist was used to evaluate mental health symptoms. RsFC between the salience and 5 other large-scale networks (i.e., default mode, dorsal attention, ventral attention, cingulo-opercular, frontoparietal) was estimated using functional neuroimaging. Linear mixed effect models, adjusting for potential confounders (e.g., income, greenspace, trauma exposure), were used to examine PM2.5-by-time interactions on rsFC.

A PM2.5-by-time interaction was significant for salience-default mode network rsFC such that youth with higher PM2.5 exhibited increased rsFC over time while youth with lower PM2.5 exhibited decreased rsFC over time (β=0.003, CI = (0.002, 0.004)). For salience network rsFC with the ventral attention and cingulo-opercular networks, there was a main effect of time (β= -0.019, CI = (-0.030, -0.008), β= -0.012, CI = (-0.023, -0.001), respectively), and a main effect of PM2.5 (β= -0.003, CI = (-0.005,-0.001), β= -0.002, CI = (-0.004, -0.001); the PM2.5-by-time interaction was not significant). These effects were associated with decreased rsFC over time, and overall lower rsFC in youth with higher as compared to PM2.5. No significant PM2.5-by-time or main effects of PM2.5 were observed for salience network rsFC with the dorsal attention and frontoparietal networks.

Increased PM2.5 exposure during childhood impacts the developmental trajectories of salience network connectivity with other neurocognitive networks, particularly those involved in attention and executive control. The salience network is typically anti-correlated with the default mode network, and thus our finding of increased salience-default mode rsFC in youth with higher PM2.5 may indicate a disruption in the equilibrium between these networks. Increased salience-default mode rsFC has also been observed in anxiety disorders. Thus, childhood air pollution exposure may increase risk of developing anxiety later in life through changes in rsFC of core neurocognitive networks. Additionally, youth with higher PM2.5 showed lower rsFC between the salience network and ventral attention and cingulo-opercular networks, suggesting dysregulation between core networks implicated in salience monitoring and attentional control. Taken together, these findings show that air pollution exposure impacts the interactions between core neurocognitive networks during the transition into adolescence, a critical period of neurodevelopment.

A8

CORTICAL PRE-SACCADIC ACTIVITY FOR VERTICALLY-DIRECTED SACCADES

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Saccades are eye movements that direct attention towards objects in the visual field. The saccade literature is dominated by studies that have relied almost entirely on horizontal saccadic tasks. A critical gap exists with reference to mechanisms of vertically directed saccades. Saccades directed downwards tend to be executed later (by 30-50 ms) than saccades directed upwards (Greene et al., 2023).

THEORY: The human head sits on top of the torso, so there are distractions from attention-grabbing movement of near-torso objects below the head (e.g., limbs). We theorized that down-directed saccades are executed/released later because they are more inhibited, than up-directed saccades. If not strongly inhibited, humans will continually (and unnecessarily) make reflexive down-directed saccades.

PURPOSE: We sought to determine how frontal lobe areas differed in the build-up of pre-saccadic neural activity, for up-, and down-directed saccades.

APPROACH: We reasonably assumed that pre-saccadic Event related potentials (ERPs) serve as indices for the preparation of saccades. We utilized an electroencephalography + electrooculography methodology to identify ERPs associated with the preparation of vertically-directed saccades.

HYPOTHESIS Given our theory that down-directed saccades are more strongly inhibited, we expected greater pre-saccadic ERP activity for down-directed, than up-directed saccade. PARTICIPANTS: 18 adult participants with no reported neurological problems participated in the experiment. A subset of 13 had frontal lobe data available for EEG analysis. The main APPARATUS was an IWORX IX-EEG (19 electrodes and VEOG) system.

PROCEDURE: Participants were presented 100 trials of an up-, or down-pointing arrow cue at the fixation point, at random. Their task was to make a saccade in the direction cued. BEHAVIOURAL RESULTS: A paired samples t test revealed that saccade reaction times were slightly slower for down-, than up-directed saccades ($p=.04$).

RESULTS: A 3 Brain Area (F3, Fz, F4) X 2 Saccade Cue (Up, Down) ANOVA revealed significantly greater absolute ERP amplitude for down-directed saccades ($p=.01$), in the interval 500ms to 300ms before the execution of saccades.

INTERPRETATION: The results suggest greater early premotor activity for down-directed saccades, possibly to overcome the strong inhibition theorized.

WHY WE CARE: Saccades occur when they are released from inhibition. Knowledge of saccade metrics in healthy individuals may inform theories of disordered saccadic processing (e.g. in schizophrenia).

A9

AMYGDALA REACTIVITY IS ASSOCIATED WITH WITH SKIN CONDUCTANCE RESPONSE IN PREDICTING FUTURE PTSD AND ANXIETY SYMPTOMS IN CHILDREN WITH TRAUMA EXPOSURE

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Background: One of the ways that sympathetic nervous activity is measured is through skin conductance response (SCR). SCR is a measure of sweat gland activity underlying the individual's physiological arousal. Recent technological advancements have provided reliable measurement of SCR using low cost and non-invasive mobile methods, such as eSense from Mindfield. We hypothesized that a higher SCR recorded in the first visit would be positively correlated with amygdala reactivity to fearful faces, and higher PTSD and anxiety symptoms on the follow-up visit.

Method: We recruited 40 children (age 9 years at first visit) for a longitudinal study in Detroit, MI. SCR was measured using a mobile application, eSense, during a trauma interview at the first visit (V0). A 3T MRI scanner was utilized to obtain amygdala reactivity to fearful and neutral faces. Anxiety and PTSD symptoms were assessed at the follow-up visit 2-3 years later, using child self-report anxiety (BASC-3) and PTSD symptoms (UCLA-PI). Children were stratified into Higher and Lower trauma groups using median split of the Violence Exposure Scale (VEXR). SCR was scored by subtracting the last 30 seconds of a 2-min baseline skin conductance recording from the maximum SCR during the trauma interview. Bilateral amygdala reactivity to fearful faces was scored by subtracting BOLD signal while children focused on a fixated cross from the BOLD signal while children watched fearful faces.

Results: Initial visit (V0) measure of trauma exposure predicted future PTSD symptoms ($r=.589$, $p<0.01$). SCR at V0 was also positively correlated with future anxiety ($r=.45$, $p<.05$) and PTSD severity ($r=.49$, $p<.05$) but only in the lower trauma group. We also found that SCR was positively correlated with bilateral amygdala reactivity, but again significant only in the lower trauma group ($r= .46$, $p<.05$). In the higher trauma group, SCR had no significant correlation to amygdala reactivity or PTSD symptoms, but was negatively correlated with anxiety symptoms ($-.53$, $p<0.01$).

Conclusions: We found that eSense SCR to a trauma interview is predictive of future clinical outcomes in children. Since amygdala reactivity increased with higher skin conductance only in lower trauma group, it may be moderating SCR's ability to predict future PTSD and anxiety symptomology. Also, SCR may be better able to predict PTSD symptoms in individuals with lower trauma because individuals with higher trauma seem to have a ceiling effect of SCR, due to already high symptoms. In general, we find that SCR can predict future PTSD and anxiety symptoms, and this is substantiated by the fact that SCR is associated with amygdala reactivity.

A10

SEX DIFFERENCES IN MONOAMINES TURNOVER AND BEHAVIORAL CORRELATES IN ZEBRAFISH: IMPLICATIONS FOR STUDYING INDIVIDUAL DIFFERENCES

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Every individual has a unique way of responding to their surroundings which determines the individual's behavior. Animal models are utilized in order to track and study behavioral differences. Zebrafish have emerged as a highly valuable model organism for investigating the biological foundation of behavior due to their biological similarities to mammals, ease of genetic manipulation and domestication, and high reproduction rate.

Novel Tank Test (NTT) is used to track exploratory behavior of zebrafish to understand the biological basis of individual differences. An animal that exhibits a greater tendency to explore a novel environment and spend more time in areas with high predation risk (such as top of the tank) is classified as bold. Conversely, an animal that displays the opposite behavioral pattern is considered shy. The boldness index is a behavioral parameter that is defined as a combination of the parameters of bottom distance and percentage of tank exploration.

In this study, we conducted the NTT followed by determination of monoamines level present in whole brain extracts of zebrafish to investigate whether there are correlations between monoamines level and behavioral differences. We performed the NTT over a period of three consecutive days, followed by euthanization and brain dissection of the fish on the sixth day. We then analyzed the levels of neurotransmitters (dopamine, serotonin, norepinephrine) and their metabolites (DOPAC, 5HIAA) using high performance liquid chromatography (HPLC).

Initially, we evaluated behavioral parameters, including distance traveled and percentage of tank explored, across sex and observed that these values were greater in males compared to females, which is consistent with prior findings. Furthermore, DOPAC/DA and 5HIAA/5HT ratios were employed as indices of dopamine (DA) and serotonin (5HT) turnover, respectively. A notable observation from our study is that there was a higher turnover of dopamine (DA) and serotonin (5HT) in males compared to females. This finding is consistent with previous reports and suggests potential sex differences in the regulation of these neurotransmitter systems.

Finally, we investigated the correlation between monoamine ratios and behavioral data. Notably, we observed a significant positive correlation between the 5HT turnover ratio and the boldness index for females on the first day of the NTT. This suggests that bolder females exhibit higher serotonin turnover. Additionally, we observed a positive correlation between the DA turnover ratio and boldness index for males on the third day of the NTT.

Taken together, our findings provide evidence that individual differences in exploratory behavior may be due to variation in monoamine levels.

A11

DIFFERENTIAL EFFECTS OF ENANTIOMERS OF THE NOVEL BENZOFURAN DERIVATIVE 1-(1-BENZOFURAN-5-YL)-2-(METHYLAMINO) PROPAN-1-ONE HYDROCHLORIDE (BK-5-MAPB) IN RATS TRAINED TO DISCRIMINATE STIMULANTS AND PSYCHEDELICS.

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3, 4-Methylenedioxymethamphetamine (MDMA) is a mixed stimulant-psychedelic/entactogen under clinical investigation for medication-assisted psychotherapy. Although this substance is used recreationally and presents some risk for abuse, phase III clinical trial outcomes indicate MDMA will likely be FDA-approved for PTSD treatment in the near future. Adverse side effects, such as anxiety and cardiovascular toxicity in some individuals, may limit its clinical use. Investigations of novel molecules with structural similarities to MDMA are underway to develop potential pharmacotherapies with comparable clinical benefits and reduced side effects. Preclinical drug discrimination assays offer exceptional utility to classify novel psychoactive substances. This study employed three rodent drug discrimination experiments to characterize the interoceptive stimulus effects of the two enantiomers of 1-(1-benzofuran-5-yl)-2-(methylamino)propan-1-one (BK-5-MAPB), a benzofuran with structural and pharmacological similarities to MDMA. In the first experiment, nine adult male Sprague-Dawley (SD) rats were trained to discriminate the stimulant, d-amphetamine (0.5 mg/kg). In experiment two, eight adult male SD rats were trained to discriminate the hallucinogen, DOM (0.5 mg/kg) from saline under a fixed ratio 20 schedule of food reinforcement. In the third experiment, eight additional male SD rats were trained to discriminate d-amphetamine (1.0 mg/kg) and MDMA (1.5 mg/kg) from saline in a three-lever drug discrimination procedure under a FR 10 schedule of food reinforcement. Stimulus substitution tests were conducted in all three experiments with (S)-BK-5-MAPB, (R)-BK-5-MAPB, and a non-racemic mixture (65% S/35% R) of BK-5-MAPB (0.32-2.54 mg/kg, IP). In the AMPH-trained rats in experiment one, both (S)- and (R)-BK-5-MAPB produced dose-dependent increases in AMPH-lever responding and full substitution at the highest dose, whereas, (S)-BK-5-MAPB produced only partial substitution and (R)-BK-5-MAPB did not substitute for DOM in experiment two. The non-racemic mixture produced partial substitution in AMPH-trained, but not DOM-trained rats. The enantiomers also produced disparate effects in rats trained to discriminate AMPH from MDMA in experiment three; (S)-BK5-MAPB fully substituted for MDMA in 5 of 6 rats tested, whereas (R)-BK-5-MAPB fully substituted for AMPH in 4 of 6 rats tested and the nonracemic mixture fully substituted for MDMA in 3 of 6 rats tested. These findings indicate (S)-BK-5-MAPB has similar interoceptive stimulus effects to both MDMA and AMPH, whereas (R)-BK-5-MAPB has primarily stimulant effects. (S)-BK-5-MAPB, either as a pure enantiomer or as a non-racemic mixture, may have promise as an MDMA-like therapeutic. Further research is required to assess the pharmacology of BK-5-MAPB, especially cardiovascular effects and potential neurotoxicity.

A12

ROLE OF VENTRAL TEGMENTAL AREA SGK1 PHOSPHORYLATION AND ACTIVITY IN DRUG-ASSOCIATED BEHAVIORS

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The mesolimbic dopamine system, which plays an important role in motivated promotes rewarding behavior, is modulated by drugs of abuse. Drugs can alter cellular activity and gene expression within the ventral tegmental area (VTA), promoting behaviors associated with addiction. Previous work in our lab found that chronic cocaine and morphine administration increased both the activity and phosphorylation (at Ser78) of serum- and glucocorticoid-inducible kinase 1 (SGK1) in the VTA. Using a viral vector strategy to overexpress a catalytically inactive SGK1 mutant (K127Q), we have found that decreasing SGK1 activity in VTA dopamine neurons is sufficient to reduce cocaine conditioned place preference (CPP), supporting that our biochemical changes are functionally relevant. However, it is unclear whether SGK1 phosphorylation also alters drug-elicited behavior. Here, we present data that decreasing VTA SGK1 phosphorylation is also sufficient to reduce drug responses. We utilized viral vectors to overexpress SGK1 mutants that either prevent (S78A) or mimic (S78D) SGK1 Ser78 phosphorylation in the VTA. We found that preventing SGK1 phosphorylation (via S78A) decreased cocaine CPP and morphine preference in a two-bottle choice assay, while mimicking S78 phosphorylation (via S78D) did not alter either behavior (n=14-21 mice/group for CPP, n=16-18 mice/group for morphine preference). Together, these data support that decreasing either VTA SGK1 catalytic activity or phosphorylation is sufficient to reduce drug-elicited behavior. Thus, we hypothesized that SGK1 pharmacological inhibition may be a translational approach to decrease drug behavior. Using Neuro2A cells, we validated that the SGK1 inhibitor GSK650349 dose-dependently decreased phosphorylation of the exclusive SGK1 substrate, NDRG. Interestingly, we also observed that GSK650349 decreased SGK1 S78 phosphorylation, suggesting pharmacological inhibition may decrease both SGK1 catalytic activity and phosphorylation. To assess whether GSK650349 could prevent drug-induced changes in VTA SGK1 activity and phosphorylation, we pretreated mice for 7 days with GSK650349 (5mg/kg, i.p.) or vehicle, then administered GSK650349 for 7 days with morphine (20mg/kg) or saline. Via western blot, we found that morphine treatment significantly increased VTA SGK1 catalytic activity and S78 phosphorylation in vehicle-treated mice as expected, while morphine mice treated with GSK650349 did not differ from saline controls (n= 11-15 mice/group). These data support that systemic GSK650349 administration is sufficient to alter SGK1 activity within the brain. We are now determining whether systemic GSK650349 can reduce drug-elicited behavior. I will investigate the effects of GSK650349 administration on cocaine locomotor sensitization, cocaine CPP, and morphine preference using a two-bottle choice test. Our preliminary data suggest that GSK650349 (5mg/kg) is sufficient to blunt cocaine-induced locomotor activity, but not cocaine CPP. Together, our data support a role for SGK1 activity and phosphorylation in drug responses and suggest that SGK1 inhibition could provide a novel avenue for therapeutic intervention.

A13

CONTROL OF EMOTION AND WAKEFULNESS BY NEUROTENSINERGIC NEURONS IN THE PARABRACHIAL NUCLEUS

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The parabrachial nucleus (PBN) is a pontine region with diverse neuronal populations that play critical roles in various physiological and behavioral processes, including breathing, emotion, and sleep/wake regulation. The PBN neurons form complex neural circuits that connect to both the forebrain and the brainstem. However, the precise identities and functions of distinct PBN subpopulations remain largely unknown. In this study, we characterized a subset of neurotensin-expressing neurons in the external lateral PBN (PBel) via RNAscope that are excitatory neurons and belong to a subset of CGRP neurons or Oprm1 neurons. Using optogenetics/chemogenetics techniques and dual retrograde tracing, we found that these neurotensinergic neurons in the PBN play a role in freezing and anxiety-like behaviors. Their projection to the emotional control regions in the forebrain, instead of the medulla, leads to indirect regulation of breathing. Moreover, chemogenetically manipulation of PBNNts neurons revealed that these neurons also play a role in promoting wakefulness and maintaining sleep architecture. Our results demonstrate that PBNNts neurons are a distinct PBN subpopulation with specific gene expression, connectivity, and function, playing an essential role in emotion and wakefulness regulation.

A14

THE HETEROGENOUS FUNCTIONS OF THE NUCLEUS OF THE SOLITARY TRACT NEURONS IN BREATHING CONTROL

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Breathing is a vital and complex behavior that is often overlooked. Breathing patterns are controlled by our brain which receives constant peripheral sensory information from the lungs and the airway. The nucleus of the solitary tract (NTS), the first relay center of our brain that receives this afferent sensory information, plays an essential role in breathing. Our research aims to understand the heterogeneity of NTS cells. To this end, we carried out a single cell RNA sequencing analysis of the mouse NTS. This analysis revealed that 19 molecularly distinct neuronal clusters make up the NTS. We then carried out a functional screen using various transgenic mouse lines to optogenetically activate different neuronal subsets in the NTS and examine their functions in controlling breathing. Our results showed that activating different neuronal populations within the NTS induced diverse breathing responses, including an ectopic inspiratory peak, apnea, a sigh, and a breathing pattern with a pronounced expiratory peak. Among these, activating a subpopulation of neurons expressing the neuropeptide gene tachykinin 1 (Tac1) induced a stereotypic response that is comparable to coughs and expiratory reflexes in human and other species. Using neuronal tracing and optogenetics, we found that these Tac1 neurons directly innervate and coordinate the medullary regions to elicit the sequential motor pattern of forceful expiratory responses. Therefore, our findings demonstrate that these NTS Tac1 neurons, as a small subpopulation of the NTS neurons, are a key component of the central pattern generator for cough-like defensive behaviors in mice. We propose that there are segregated neuronal circuits through different molecularly distinct NTS neuronal populations that serve similarly specific roles in other respiratory functions.

A15

CHARACTERIZATION OF OXYTOCIN RECEPTOR BINDING DENSITY IN THE OXTR-ICRE RAT LINE TARGETING BRAIN REGIONS ASSOCIATED WITH SOCIAL BEHAVIOR

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The neuropeptide oxytocin (OXT) regulates various social behaviors through the activation of oxytocin receptors (OXTR) in the brain. However, little is known about the neural pathways by which OXTR activation regulates these behaviors. To study this, we recently generated the first OXTR-iCre rat line. The OXTR-iCre rat line expresses Cre recombinase in all cells that express OXTR. We confirmed the functional expression of Cre in OXTR-expressing cells in this line. Now, we aim to verify that the insertion of Cre does not affect OXTR expression in the brain. To this end, we measured OXTR binding density in six brain regions that are involved in the regulation of social behaviors, that express OXTR, and that show existing age and/or sex differences in OXTR binding density. These brain regions include the Nucleus Accumbens (NAc), Bed Nucleus of the Stria Terminalis (BNST), Anterior (aVMH) and Posterior (pVMH) Ventromedial Hypothalamus, Posterodorsal (MePD), and Posteroventral Medial Amygdala (MePV). We hypothesized that Cre does not have an effect on OXTR binding density and expected to find similar OXTR binding density levels as well as similar age (juvenile versus adult) and sex differences between OXTR-iCre and Wild Type (WT) rats (n=8/group). Through receptor autoradiography, we applied a radiolabeled ligand that selectively binds to OXTR. We then digitized the resulting autoradiograms and compared relative density measurements from the targeted brain region. The darkness of these samples was used as an approximation of the relative OXTR binding density of the region. We found that OXTR-iCre rats have lower OXTR binding than their age- and sex-matched WT counterparts in 4/6 brain regions analyzed, namely the NAc, BNST, aVMH, pVMH, and MePD. However, this effect was limited to one age and/or sex in the Nac, BNST, and MePD. This could mean that Cre insertion affects the expression of the OXTR gene inconsistently across age and sex. In the future, we plan to compare OXTR gene expression and viability of these cells using qPCR and Western Blots respectively. We were able to confirm existing age and sex differences in OXTR binding density in the BNST and aVMH but not in the NAc, pVMH, or MeA. This may be due to differences in experimental design between our study and the previous study that resulted in different OXTR binding density measurements. To replicate previous findings, we may repeat this experiment with juveniles group-housed until perfusions at exactly 35 days of age and adults pair-housed until perfusions at exactly 84 days of age. In conclusion, this characterization lays the foundation for the use of this unique OXTR-iCre rat line to study the anatomical and functional properties of OXTR-expressing cells in the brain through the use of Cre-dependent chemogenetic, optogenetic, and viral tools.

A16

NOVEL BENZOFURAN AND BENZOTHIOPHENE ANALOGS ARE MONOAMINE RELEASING AGENTS THAT SUBSTITUTE FOR THE DISCRIMINATIVE STIMULUS EFFECTS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA)

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Novel psychoactive substances (NPS) are popular on the illicit drug market and present a global public health concern. Structurally similar to 3,4-methylenedioxymethamphetamine (MDMA), benzofurans represent the third most popular group of NPS on the illicit drug market. Although phase III clinical trials with MDMA have shown therapeutic benefits in medication-assisted psychotherapy for post-traumatic stress disorder (PTSD), cardiovascular and neurotoxicity risks may limit its clinical use for some individuals. Preclinical investigations of NPS offer an opportunity for the discovery of alternative pharmacotherapies. Drug discrimination is a behavioral assay with pharmacological specificity for characterizing in vivo drug actions in the central nervous system. As part of an ongoing study of benzofuran and benzothiophene molecules in rodent drug discrimination, these experiments assessed the discriminative stimulus effects of the (S)- and (R)- enantiomers of [1-(1-benzofuran-6-yl)butan-2-yl](methyl)amine (6-MBPB) and [1-(1-benzothiophen-6-yl)butan-2-yl](methyl)amine (6-MBPBT). Twenty-four male Sprague-Dawley rats were trained to discriminate MDMA (1.5 mg/kg, IP) from saline in a two-lever operant drug discrimination procedure under a fixed ratio 20 schedule of food reinforcement. Stimulus substitution tests were conducted in subgroups of rats (N=8-12) with (S)- and (R)-6-MBPB, and with (S)- and (R)- 6-MBPBT (1.34-10.7 umol/kg, IP). In separate experiments, monoamine release and uptake inhibition at SERT, DAT, and NET were assayed using rat synaptosomes and [3H]5-HT or [3H]MPP+ as a substrate. Drug discrimination study results showed dose-dependent increases in MDMA-lever responding and full substitution with both (S)- and (R)-6-MBPB at 5.35 and 10.7 umol/kg. (S)- and (R)-6-MBPBT produced nearly complete substitution at 10.7 umol/kg. Pharmacological assays indicated S-isomers are fully efficacious releasers at DAT, NET, and SERT, whereas the R-isomers are fully efficacious at SERT, but lower efficacy at NET. Differences between the potencies of the benzofurans and analogous benzothiophenes in the drug discrimination procedure did not appear to be driven by their potencies at monoamine transporters, and may instead reflect kinetic differences, such as partitioning between plasma and brain. These results provide further evidence that sulfur can act as a bioisostere for oxygen in MDMA-like molecules.

B7

NEUROTENSIN EXPRESSING LATERAL HYPOTHALAMIC NEURONS ALLEVIATE NEUROPATHIC AND INFLAMMATORY PAIN VIA NTS SIGNALING

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The plague of chronic pain has fueled the U.S. opioid epidemic, creating a critical need for novel pain therapeutics that do not cause dependence. In preclinical models, central treatment with the neuropeptide Neurotensin (Nts) or Nts receptor agonists promotes analgesia, suggesting that augmenting Nts system signaling may be useful to treat pain. However, the lack of clarity of the endogenous Nts mechanisms regulating pain has hindered understanding of how to leverage the Nts system for pain relief. The objective of this study was to determine whether the large population of lateral hypothalamic area (LHA) neurons expressing Nts (referred to as LHANts neurons) contribute to analgesia. We hypothesized that activating LHANts neurons can alleviate chronic pain in an Nts-dependent manner. To test this, we injected NtsCre mice in the LHA with AAVs to cre-dependently express either mCherry (Control) or excitatory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in LHANts neurons, permitting their activation after treatment with the DREADD ligand clozapine N-oxide (CNO, 0.3 mg/kg, i.p.). We then measured how DREADD-activation of LHANts neurons impacts acute thermal pain (using the hot plate test), spared nerve injury (SNI) pain or complete Freund's adjuvant (CFA)-induced inflammatory pain measured using the von Frey test. Activating LHANts neurons had no effect on thermal pain responses in naïve mice. By contrast, SNI-induced pain hypersensitivity (indicated by reduced paw withdrawal threshold at 7- and 28-days post-injury) was completely reversed by CNO-mediated activation of LHANts neurons compared to VEH control. In CFA-treated mice (a model of inflammatory pain), CNO-activating LHANts neurons also relieved pain hypersensitivity, increasing paw withdrawal threshold by 30 mins post treatment that gradually reduced to baseline in 5 hours. However, pretreatment with the brain permeable Nts receptor pan-antagonist SR142948 (1mg/kg, i.p, 30 min before VEH/CNO) blocked CNO-mediated analgesia, indicating that LHANts neurons alleviate chronic pain in an Nts-dependent manner. Intriguingly, RNAscope analysis revealed that Nts mRNA expression was increased in the LHA in response to CFA and SNI, suggesting that prolonged pain may increase endogenous Nts, with potential to provide analgesia. Taken together these data suggest that activation of LHANts neurons alleviates neuropathic and inflammatory pain via Nts signaling, and augmenting Nts signaling via these neurons could hold promise for treating pain.

B8

TO PLAY OR NOT TO PLAY? UNDERSTANDING OPTIMAL CONDITIONS FOR STUDYING SOCIAL PLAY BEHAVIOR IN DIFFERENT LABORATORY RAT STRAINS

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Social play, or "rough-and-tumble" play, is a common social behavior observed in juveniles of many mammalian species, including rats and humans. Social play is vital to the development of emotional, social, and cognitive skills, and contributes to appropriate social interactions and behaviors later in life. Engagement in social play also builds social awareness and helps establish flexible social problem-solving skills. Children diagnosed with autism spectrum disorder or schizophrenia show decreased involvement in social play behaviors with their peers compared to typically developing children. Children with these disorders report that they find social interactions less pleasant than other non-social interactions, such as riding a bike or eating. A lack of social play can reduce the ability of autistic individuals to appropriately navigate social and emotional situations later in life. Despite the documented importance of social play, little is known about the brain mechanisms regulating this behavior. A better understanding of these mechanisms could lead to developing therapeutics that aim to restore deficits in social play. Considering that juvenile rats naturally show social play, rats are the model species to study social play in laboratories. Nevertheless, there is limited comprehensive knowledge on how to best test social play for commonly used rat strains. Therefore, this study focused on optimizing procedures for studying social play in two common laboratory rat strains: Long-Evans and Sprague Dawley. All experiments utilized 10-minute social play tests, where a sex-, age- and strain-matched stimulus rat was introduced into an experimental rat's home-cage. We determined the effects of two factors on social play behavior, namely the familiarity level of the stimulus rat (i.e., familiar vs unfamiliar) and the length of social isolation before testing (2-h vs 24-h). Overall, our goal is to provide recommendations for optimal conditions to measure social play behaviors in different rat strains, so researchers can more efficiently work toward the big-picture goal of understanding the brain mechanisms regulating social play behavior.

B9

IDENTIFYING NEURAL CORRELATES OF INDIVIDUAL DIFFERENCES IN ADULT ZEBRAFISH BEHAVIOR COMBINING IN-SITU HYBRIDIZATION CHAIN REACTION WITH ADULT ZEBRAFISH BRAIN ATLAS AND BRAINGLOBE

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Individual behavior is complex and can vary widely, even among members of the same species. Behavioral differences have been observed across wide range of taxa, including humans, rodents, and fish. However, the biological mechanisms that underlie these differences are not fully understood. To explore the neural mechanisms that underpin behavioral differences, we use adult zebrafish as a model. Previously, we have identified four distinct behavioral types in adult zebrafish when exploring a novel environment.

To gain a better understanding of the neural basis of these differences, we are developing tools for whole-brain activity mapping. We are using situ hybridization chain reaction (HCR) to detect the expression of cfos, an immediate early gene, as a means of labeling active neurons. To visualize brain-wide c-fos expression, we are utilizing a tissue clearing technique and light sheet microscopy to generate high resolution images. Further, we integrated the recently developed adult zebrafish brain atlas (AZBA) into the BrainGlobe computational environment, that includes image registration, visualization tools, and CellFinder, a deep learning approach to cell identification. This integration enables us to parcellate images into various brain regions. We trained CellFinder to detect c-fos positive cells with high accuracy (96%), which we used to identify the peak c-fos expression in the brain following exposure to the novel tank. With this approach, we will identify the neural mechanisms underlying individual differences in behavior.

B10

ESTROGEN MEDIATES MELANIN CONCENTRATING HORMONE EXPRRESSING CELLS TO CONTROL TIME-DEPENDENT MOTIVATED FOOD SEEKING

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Decisions on when to search out and eat food are mediated by timing mechanisms in the brain. However, little is known about how mechanisms controlling the perception of time (in the seconds to minutes range) interact with biological systems controlling food intake. Our laboratory was the first to demonstrate that stimulation of the lateral hypothalamic area (LHA) expressing feeding signal, Melanin Concentrating Hormone (MCH), enhanced temporally dependent food-seeking in female rats. Strikingly, this effect was dependent on the estrus cycle stage. In female rats, estrogen levels fluctuate across four phases: estrogen is relatively low in metestrus and diestrus (M/D) and higher during proestrus and estrus (P/E). Only when rats were in M/D (i.e., low levels of gonadal hormones) did stimulation of MCH expressing cells enhance temporally dependent food-seeking. In the current study, we isolated the effects of estrogen in time-dependent motivated food-seeking by removing the ovaries through ovariectomy (OVX) before testing the effects of excitation of LHA MCH expressing cells. Moreover, we examined a specific circuit by targeting only LHA MCH cells that project to the nucleus accumbens (NAc), an area of the brain thought to be critically important for time-dependent motivated food-seeking. Overall, our findings reveal the neural and hormonal mechanisms controlling time-dependent food-seeking including independent functions of estrogen and complex interactions of this gonadal hormone on functionality of LHA MCH cells that project to the NAc. Thus, we have elucidated a potential cellular mechanism of differences in food-seeking behaviors in female rats that are controlled by gonadal hormones.

B11

REGULATION OF STRESS AND ANXIETY IN A MOUSE MODEL OF HORMONAL CONTRACEPTIVES

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Hormonal contraceptives (HCs) are a critical part of healthcare, with broad health and economic benefits. For many users, HCs have beneficial mood effects, with decreased premenstrual mood changes and overall better mood. Yet for 4-10% of people, HCs trigger adverse mood effects and increased risk for depression. Here, we used a mouse model of oral contraceptive exposure, newly developed in our laboratory, to identify how different HC formulations regulate stress responses and contribute to the vulnerability to stress-induced behavioral changes. Female C57Bl6 were given ethinyl estradiol (EE, 0.02µg) and a progestin – either the androgenic levonorgestrel (LVNG, 0.75µg) or the anti-androgenic drospirenone (DRSP, 3.75µg) – daily in 0.25mL 10% sucrose; control animals received 0.25mL of 10% sucrose. At these doses, contraceptive hormones have no gross effects on locomotor activity and do not increase anxiety-like behavior. However, they decrease sucrose preference, suggesting specific anhedonic-like effects, and affect risk-assessment behavior. In parallel with findings from people using HCs, mice treated with EE+LVNG, but not DRSP, had significantly blunted stress-induced corticosterone. We investigated the interactions of HCs and stress using immunohistochemistry to identify HC-induced changes in glucocorticoid and mineralocorticoid receptors, and stress-induced signaling pathways. Together these findings demonstrate that the interaction of HCs with the HPA axis and stress-related signaling are key mechanisms for vulnerability and resilience to stress-induced depression. Identifying individual differences in stress responsivity may help predict which individuals will benefit from which HC formulations, improving personalized medicine.

B12

DIETARY PROBIOTIC SUPPLEMENTS ATTENUATE RATE SUPPRESSANT EFFECTS OF MDMA IN MALE RATS TRAINED ON A DRL 18 REINFORCEMENT SCHEDULE.

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The recent emergence of research focused on gut microbiome connections to mental health offers an exciting new prospect for the development of complementary treatments for substance use disorders. Reduced executive functioning and increased impulsivity is associated with psychostimulant abuse. The current study implemented a DRL 18 reinforcement schedule to evaluate whether probiotic supplements would alter drug effects on impulsive action in rats. Eight adult male Sprague-Dawley rats were trained five days a week for several months on a DRL 18 schedule of food reinforcement until responding was stable. Rats were subsequently assigned to two treatment groups, matched on performance measures, and fed daily supplements of an Align® probiotic/Nutella® mixture or Nutella® alone for three months, while training continued three days a week and fecal samples were collected weekly. All rats were assessed following acute injections of saline or MDMA (3 mg/kg) at week 7, 24 hours after binge dosing (5 mg/kg x 4) at week 8, and again after acute injections at week 11. Performance measures remained stable and equivalent between groups throughout dietary treatment prior to injections. In probiotic-fed animals, acute MDMA treatment shifted the interresponse time distribution to the left compared to saline injections, whereas animals fed the control diet displayed an overall response suppression following MDMA injections. These effects did not persist 24 hours after acute or binge treatment at weeks 7 and 8, but response rate suppression did persist in the control diet rats 24 hours after MDMA injection in week 11. While fecal sample analysis is currently ongoing, these behavioral results indicate MDMA’s effects on impulsive action may be attenuated by probiotic treatments. In conclusion, the DRL 18 schedule shows promise as a predictive tool to evaluate the effects of gut microbiome manipulations as a means of attenuating drug-induced behavioral changes.

B13

EXAMINING THE BEHAVIORAL AND NEUROBIOLOGICAL CORRELATES OF BINGE EATING THROUGH AN ANALYSIS OF LICKING MICROSTRUCTURE AND C-FOS EXPRESSION

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Binge eating (BE) reflects a pathologic over consumption of palatable food that is present in a variety of eating disorders. However, the specific behavioral and neurobiological mechanisms underlying BE remain largely unknown. In this study, we used an individual differences rat model of BE, through which phenotypes of binge eating prone (BEP) rats were revealed following intermittent access to palatable food. Once identified, BEP and non-BEP rats received short-term consumption testing with a palatable food solution (sucrose). Following these tests, the interval between individual licks were quantified using licking microstructure. Licking microstructure allows for the evaluation of the pre-ingestive taste and post-ingestive variables that drive food seeking, consumption, and the termination of feeding. This analysis revealed that BEP rats displayed a pattern of ingestive behavior consistent with an increase in the hedonic evaluation of the palatable sucrose solution and increased post-ingestive inhibition. Following the final short-term consumption test, rats were euthanized to enable activity-dependent analysis using the immediate early gene marker for neuronal activity, c-fos. Differences in c-fos activity between BEP and non-BEP rats in response to palatable food exposure were examined, with a particular emphasis on activity in the lateral habenula and ventral mesencephalon—key structures driving both the hedonic and rewarding features palatable food intake. Overall, our findings suggest that a predisposition for an increased hedonic evaluation of palatable food together with altered post-ingestive negative feedback and aberrant activity within reward circuitry may underlie BE.

B14

THE NEURAL AND AUTONOMIC EFFECTS OF NON-INVASIVE VAGUS NERVE STIMULATION DURING ATTENTIONAL PROCESSES: AN EXAMINATION OF THE DOSE DURATION RESPONSE

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Background: Transcutaneous auricular vagus nerve stimulation (taVNS) is a brain stimulation candidate intervention tool for psychiatric disorders (e.g., posttraumatic stress disorder) that may impact transdiagnostic disorder-relevant processes (e.g., inflexible stress responding and cognitive processing) by directly modulating mechanistic vagal tone. TaVNS has many advantages over other technologies, including that it is non-invasive, affordable, and safe enough to implement at home or in therapy/clinical settings without immediate MD oversight. A major limitation to the development of therapeutic taVNS, meanwhile, is unestablished optimal stimulation duration, dose response relationships, and mechanisms of effects. Method: The current research aimed to establish the dose-response curve of taVNS on vagally-mediated physiological indicators (EEG, heart rate, and skin conductance) during cognitive engagement (orienting of attention in a steady-state visually evoked potential task; target detection in an oddball P300 task). 28 healthy participants received 1 of 5 sham-controlled taVNS durations (15-75 mins) increasing in 15-minute doses delivered at 200% perceptual threshold (500µs pulse width, 25Hz frequency in 60 second on/off trains). Cognitive tasks were completed prior to taVNS and concurrent with the last 10 minutes of stimulation. A range of curve estimation models are fit to each physiological indicator measured during tasks. Results: HRV data were associated with significant linear and logarithmic fit (ps <.05) suggesting greater doses modulate vagal tone. The oddball P300 event-related potential data were not associated with significant model fit (ps >.05). Skin conductance and steady-state EEG data are being prepared for analyses. Conclusions: Findings indicate that greater doses, especially those outside the typical range (i.e., 60-75 minutes) of taVNS result in improved vagal balance. Lack of asymptote to the data suggest greater dose duration of taVNS may be warranted. Neural indices of attention were not modulated by taVNS dose duration, suggesting there may be differential effects on gradual (autonomic) vs. instantaneous (electrocortical) processes. A more motivationally engaging task (e.g., fear learning) and evaluation of orienting/steady-state data also may help disentangle taVNS cognitive-affective effects. Once the dose response curve is established across each psychophysiological measure, future research is warranted to optimize taVNS for clinical intervention.

B15

TRAUMA FROM THE EYE OF THE BEHOLDER

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Background: This study focused on child and caregivers report of trauma exposure and PTSD symptoms to examine discrepancies in reporting. We further examined which reports aligned more closely with threat-related neurobiological biomarkers in the child – specifically, amygdala activation to threat cues and fear-potentiated startle (FPS). We hypothesized that these would be associated with the child report.

Methods: N=43 dyads of caregiver/child participants aged 8-13 years old. Trauma exposure was measured using Trauma Exposure Screening Inventory (TESI). PTSD symptoms were assessed using the UCLA PTSD Reaction Index. Anxiety and Depression symptoms were assessed using the Behavioral Assessment System-3 (BASC-3). All scales included child and caregiver report that were administered in separate rooms. FPS was measured via eyeblink electromyographic (EMG) responses during a fear conditioning task. A reinforced conditioned stimulus (CS+, threat cue) was paired with an aversive air blast at 100% reinforcement rate. The non-reinforced stimulus (CS-, safety cue) was not paired with the aversive air blast. We obtained functional magnetic resonance imaging (fMRI) imaging from the children viewing fearful and neutral faces.

Results: Our analysis indicated that children's report of their own trauma was positively correlated with their own report of PTSD symptoms, r= .45, p= .006. Similarly, parents' report of their child's trauma strongly correlated with their report of child PTSD symptoms, r = .56, p= .001. However, there was a parent/child report discrepancy between how much trauma occurred and the severity of those symptoms. Parents reported that their child experienced more trauma exposure than the child reported, F= 4.54, p= .039. Children reported higher symptom severity for themselves than the parents reported, F= 7.69, p= .010. Child reported anxiety was positively correlated with FPS to threat (CS+), r= .55, p< .001 and safety (CS-), r= .44, p= .013. Lastly, child reported trauma was also positively correlated, r= .33, p= .033 with bilateral amygdala activity to faces.

Conclusion: These results highlight the consistency between neurobiological biomarkers of trauma-related responses of the child and the child-reported symptoms and trauma. Importantly, parental reports were not associated with child report of their own trauma exposure, symptoms, or neurobiology. These data support the importance of collecting self-reported trauma information from children, especially in biomarker research. Future longitudinal work should establish the predictive value of self-reported data and biomarkers for later psychopathology for early interventions during development.

B16

INTERMITTENT MORPHINE ACCESS THROUGHOUT GESTATION IMPAIRS MOUSE MATERNAL BEHAVIOR DEVELOPMENT AND ENHANCES ANXIETY OUTCOMES

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Background: The opioid epidemic has wreaked havoc in the United States over the past few decades. Specifically for pregnant women, opioid use disorder has quadrupled (CDC, 2018). Yet, the physiological effects of opiates on pregnant women, and their infants, are not fully understood. Literature within the field describes that maternal behavior is modulated by the endogenous opioid system, which is also a target for drugs of abuse, like morphine. It is likely that neuronal circuits involved with maternal behavior and rewarding feelings of drug intake may be shared. Clinical studies suggest that chronic morphine use leads to opioid receptor sensitization and reduced responses to infant cues (Wallin et al. 2021; Miranda-Paiva et al. 2001). In rodents, morphine use in late gestation led to decreased preference for pup odors, prolonged the latency of last pup retrieval, and increased non-maternal activities, such as self-grooming and digging (Wallin, et al. 2021; Slamberová & Szilágyi, 2001). The purpose of this study is to evaluate if an intermittent, voluntary regimen of morphine exposure started prior to conception and continued throughout gestation - mimicking human patterns of drug taking - differentially alters maternal behavior. We hypothesize that voluntary consumption of morphine by female mice prior to the start of breeding will interfere with their development of maternal behavior. This study deviates from previous studies in the field because morphine consumption begins much earlier with hopes of reproducing previous rodent study results and human observations in a translationally relevant fashion. Methods: Female mice (9-10 weeks of age) began limited access morphine drinking (0.2 mg/ml) (0.2% morphine in sucrose) two weeks prior to breeding and continued consumption until pups were weaned. The experimental group was given single bottle access to the morphine in sucrose solution, while the control group was given access to sucrose only. Dams were longitudinally assessed for anxiety with an open field test, and maternal behaviors, including pup retrieval, olfactory discrimination, and licking and nesting. Results: Pup retrieval time was decreased when measured at mid (4) compared to early (1-2) postnatal days (PD) in control dams, reflective of maternal learning, which was absent in morphine exposed dams. Morphine dams also displayed reduced licking and nesting behavior during pup retrieval, spent less time seeking pup olfaction cues indicating a decreased preference for their offspring, and showed greater anxiety-like behavior compared to their control counterparts. Conclusion: These data support the hypothesis suggesting a robust negative impact of intermittent, chronic morphine intake on maternal behavior development that may involve mood dysregulation. More research is necessary to determine the specific neurobiological mechanisms that lead to these changes in maternal behavior. One day this research could inform treatments that improve maternal and fetal outcomes for opioid users.

A17

UBIQUITIN-PROTEIN LIGASE PARKIN IN METHAMPHETAMINE USE DISORDER

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Background

In the United States, there are close to 1,000,000 people with methamphetamine (METH) use disorder (MUD). Despite numerous clinical trials conducted to date, there is no FDA-approved medication for MUD, needed especially for people who abuse METH heavily as they are at high risk for METH overdose. Our previous study demonstrated that overexpression of a ubiquitin-protein ligase parkin in the nucleus accumbens (NAc) decreased METH intake and relapse to METH seeking in rat model of heavy METH use. The goal of the current study was to elucidate molecular pathways underlying the anti-addictive properties of parkin in this model.

Methods

Parkin was overexpressed in NAc neurons of young adult male rats utilizing adeno-associated viral vector AAV2/6. Subsequently, parkin-overexpressing (PO) and wild-type (WT) rats self-administer METH during 15h-long sessions for 10 consecutive days on an increasing fixed-ratio schedule (FR1-5). All rats were withdrawn from METH for 10 days. Half of the rats were euthanized; another half was reinstated to seek METH and euthanized 24h later. Discovery proteomics and GSEA analysis were employed to generate NAc proteomes and analyze the data, respectively.

Results

GSEA analysis of the proteomic data revealed that the EIF2 pathway was the only pathway altered in all PO rats as compared to WT rats. Major biological processes altered by parkin overexpression in the NAc of METH-withdrawn rats were RNA processing, processes involved in tonic motor seizures, and GPCR signaling. Leading-edge proteins from the third group were proteins mediating synaptic vesicle docking and exocytosis, and proteins mediating loading glutamate to the storage vesicles. In rats that relapsed to METH seeking, the most altered cluster of pathways was Notch response to chemical hypoxia. The leading-edge proteins within this cluster were proteins belonging the 19S proteasome that are involved in Notch, NFT2L2, TNFR2, p53, and Hedgehog pathway. In adult brain, these pathways mediate DNA and brain tissue repair, maintenance of plasticity, inflammation, and antioxidant and anti-apoptotic processes.

Conclusion

Our results suggest that pathways mediating stress and inflammatory responses underlie anti-addictive properties of parkin.

A18

ORGANIZATIONAL AND ACTIVATIONAL IMPACT OF OVARIAN HORMONES ON FEMALE RAT BINGE EATING BEHAVIOR

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Binge eating (BE) is a maladaptive behavior involving the over consumption of palatable food (PF) in a discrete period and is a core feature of a range of eating disorders. Studies suggest that the preference for PF is stronger in females than males in both animals and humans and that this sex difference may be partially due to ovarian hormones. Lower levels of estradiol are associated with increased PF intake in women and adult female rats. However, relatively little is known about the extent to which ovarian hormones during earlier periods of development influence PF intake. In this study, we used an individual differences model of binge eating, whereby differences in susceptibility to overeating of PF are revealed following a series of intermittent access tests with palatable food. This typically reveals distinct cohorts of rats that are consistently binge eating prone (BEP), resistant (BER), or neutral (BEN). To examine the impact of estrogen on conferring risk for BE, female rats were pre-pubertally ovariectomized (OVX). The prevalence of BEP, BER, and BEN phenotypes was examined in OVX rats and compared to rats that received estrogen replacement throughout puberty and into adulthood. In female rats that received pre-pubertal OVX in the absence of estrogen, we predict increased proportion of BEP rats. Conversely, in rats that received OVX and estrogen replacement during puberty, we anticipate decreased adult rates of BEP in this cohort. Overall, this study provides insight into the hormonal basis underlying the organizational and developmental risk for BE.

A19

ROLE OF ENTORHINAL CORTEX NEURONS IN THE CONSOLIDATION AND/OR RECALL OF A COCAINE-CONTEXT MEMORY

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Cocaine addiction is a critical health burden in the US. Cocaine alters the brain reward circuitry, including the nucleus accumbens (NAc), leading to dysfunctional processing of reward and motivation underlying addiction. Glutamatergic neuronal pathways synapse onto NAc neurons to mediate cocaine reward. The lateral entorhinal cortex (LEC), a brain region important for memory encoding and retrieval, also sends projection neurons to the NAc1-3, suggesting that glutamatergic projections from LEC to NAc may play an important role in mediating cocaine's rewarding effects and development of addiction.

Supporting this, LEC is activated by cocaine cues in cocaine self-administering mice2 and cocaine-dependent humans3. However, the role of LEC, and specifically LEC neurons that project to NAc (LEC-NAc), in mediating cocaine reward is currently unknown. We have preliminary evidence showing that LEC- NAc neurons are necessary for the expression of cocaine reward, yet it's unclear whether LEC-NAc is necessary for the encoding and/or retrieval of a cocaine associative memory.

A20

USING MACHINE LEARNING TO IDENTIFY INDIVIDUAL DIFFERENCES IN FEAR RESPONSES AND MEMORY IN ZEBRAFISH (DANIO RERIO)

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Individual differences in fear responses can contribute to survival and influence evolutionary adaptation. However, the underlying mechanisms for these differences are not fully understood and likely involve both genetic and environmental factors. Here, we identified zebrafish individual differences in fear and memory-related responses by developing a machine learning model to automate the analysis of behavior and comparing 4 different strains (AB, TU, TL, WIK) and both sexes. Fish (n = 432) were recorded using an automated system (Zantiks AD) and tracked using DeepLabCut (head, trunk, and tail). Fear was elicited by exposing fish to alarm substance (a fear cue released by conspecifics to alert danger), and the next day, they were reintroduced to the same place to assess memory. To automate behavioral assessment and increase throughput, we created a random forest model to identify different behaviors by labeling over seventy thousand frames with posture information (x and y coordinates of 3 points) and the associated behaviors (e.g., freezing, erratic movement). This approach resulted in a low error rate (2.8%). Subsequent clustering analysis found individual differences in how zebrafish responses to fear-inducing stimuli and fear-related memory: (1) low response to the fear cue, (2) increases in overall burst swimming and erratic movement (3) high freezing combined with elevated burst and erratic movement, (4) high freezing responses followed by normal swimming. Distribution across groups was influenced by genetics: TL fish were mostly represented in the high freezing clusters (3 or 4), and TU fish were mostly found in the low fear response cluster (1). The identification of individual differences in fear responses and memory in zebrafish represents a significant advancement in the field, as this is the first time these differences are identified in this species. These findings not only demonstrate the utility of zebrafish as a model for studying fear-related behaviors but also open the door to identifying the neural and molecular mechanisms underlying these individual differences. Future work mapping the brain regions involved in these behavioral clusters will shed light on the specific pathways involved in fear processing.

A21

DISRUPTING COCAINE-SEEKING BY DEVALUING MEMORIES OF COCAINE REWARD THROUGH MESOLIMBIC CIRCUITRY

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Cocaine is a readily abused psychoactive drug; deaths from overdosing have risen to ~20K/year and annual healthcare costs increased to over $700 million. Unfortunately, there is a lack of effective treatment strategies and accordingly many previous users display relapse to cocaine-taking behavior, particularly when exposed to drug-related cues or contextual stimuli, even after long periods of abstinence. Thus, there is a critical need to develop strategies to disrupt drug-related activities. We have developed an approach in which memories associated with cocaine-seeking are devalued by pairing these memories with gastric malaise. This approach results in a marked reduction (>50% reduction) in cocaine-seeking behavior. Furthermore, we have begun to isolate the brain circuitry underlying this phenomenon. This was achieved by a dual-viral intersectional strategy, in which a retrograde Cre-recombinase virus was placed into nucleus accumbens (NAc), and a Cre-dependent inhibitory DREADD, hM4Di, injected into the ventral tegmental area (VTA). This enabled silencing of VTA cells projecting to NAc when rats were injected with the actuator, clozapine-N-oxide (CNO). Thus, we will examine the necessity of VTA to NAc circuitry in underlying memory devaluation effects that disrupt cocaine-seeking. Overall, these studies lay the foundation to develop novel approaches to attenuate addictive behaviors.

A22

PAIRING OPTOGENETIC STIMULATION OF THE CENTRAL AMYGDALA WITH A CUE AMPLIFIES 'WANTING' MOTIVATION

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In this study, we paired central amygdala (CeA) activation with either an auditory cue (conditioned stimulus) which immediately preceded a sucrose reward, or with the sucrose reward itself to determine which CeA pairing would be more effective at amplifying ‘wanting’ motivation. Here we are building off of previous research that has shown that CeA activation can enhance incentive motivation for paired rewards. Our results suggest that pairing CeA optogenetic activation with the auditory cue enhanced ‘wanting’ motivation greater than CeA activation paired with the sucrose reward itself. These findings help to further our understanding of the role of cues in incentive motivation and how CeA neural systems may further be involved in disorders such as addiction.

A23

ROSTRAL AND CAUDAL VENTRAL PALLIDUM GABA NEURONS DIFFERENTIALLY CONTROL DISGUST AND AVERSION

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The ventral pallidum (VP) is a unique structure within the mesocorticolimbic motivation system because of its implication in both the 'wanting' and 'liking' of rewards, as it contains a hedonic hotspot that is responsible for the generation of pleasure. Its heterogeneity in neuronal makeup includes largely non-overlapping populations of neurons with opposing functions. In this study, we look into the VP's GABAergic neurons to assess whether their inhibition controls 'liking' and 'wanting' of sucrose rewards differentially within the rostral and caudal VP. We used optogenetics with an inhibitory virus in transgenic GAD1-Cre rats in order to inhibit VPGABA neurons while testing animals on measures of 'liking' vs. 'wanting'. Measures of subjective 'liking' were collected with the taste reactivity test, where orofacial reactions were quantified and categorized into hedonic, negative, or neutral. For 'wanting', we used various tests such as operant two-choice, self-stimulation, and shock-rod aversion to measure different aspects of incentive salience. We found that positive hedonic impact was significantly suppressed by inhibition of GABAergic neurons within the posterior, but not anterior VP. Findings from the taste reactivity test suggest that suppression of GABAergic neurons in the hedonic hotspot of the pVP generates 'disgust', which physiologically sets this pleasure hotspot apart from all others. In determining the role of caudal versus rostral VPGABA neurons in motivation, results from behavioral testing reveal that GABAergic neurons within the rostral and caudal VP differentially contribute to aversive motivation. These findings elucidate the neural mechanisms behind our motivational and affective systems as they become dysregulated in mood disorders.

A24

SINGLE PROLONGED STRESS OR NALOXONE-PRECIPITATED MORPHINE WITHDRAWAL AFFECTS CONDITIONED FEAR LEARNING USING FEAR-POTENTIATED STARTLE IN RATS BUT THEIR COMBINATION IS NOT ADDITIVE.

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Opioid use disorder (OUD) is highly comorbid with posttraumatic stress disorder (PTSD). Great effort has been made to investigate and models the effects of traumatic stress on opioid-taking and related behaviors. Fewer investigations have explored the reversed order; in other words, how does opioid use affect fear learning and reactions to traumatic stress. Opioids can produce profound changes in associative learning mechanisms, leading to dependence and altered fear learning following stress exposure . Recent rodent studies have shown that opioid taking and withdrawal may lead to a more robust or more sensitized fear acquisition. The goals of our current study were three-fold. (1) Validate the generalizability of opioid withdrawal effects on fear learning using a translational measurement sensitive to fear-like states: the fear potentiated startle model. (2) Use fear potentiated startle to determine opioid withdrawal effects on fear extinction, an amygdala and prefrontal cortex dependent process . (3) Investigate the combined effects of opioid withdrawal and traumatic stress on fear learning and extinction. In this study, we used Sprague Dawley rats to investigate the individual and combined effects of both escalating morphine with naloxone-precipitated withdrawal and single prolonged stress (SPS, a model of posttraumatic stress in rodents) on fear acquisition and fear extinction.

RESULTS: We found that morphine withdrawal produced transient deficits in extinction learning, SPS produced sustained extinction retention deficits. However, there was no additive or otherwise combined effect of morphine-withdrawal and SPS.

FUTURE DIRECTIONS: Planned future studies include the use of chemogenetics to investigate the contribution of a locus coeruleus to basolateral amygdala circuit in producing the SPS induced extinction retention deficit in both males and females to begin investigations into the neurobiology of this behavior. Additionally, we will implement tests of renewal of extinguished fear in SPS rats to further validate SPS as a model of traumatic stress.

A25

THE INTERACTION OF EARLY LIFE STRESS AND HISTORY OF SWEET FLUID EXPOSURE ON MOTIVATION FOR ALCOHOL

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Early life stress and chronic stressors are associated with high alcohol consumption and binge drinking. The stress promotes consumption of sweet foods/fluids which may decrease effects of stress on biological parameters such as stress hormone levels and psychological parameters such as anxiety. The purpose of this study was to evaluate how early life stress in Sprague–Dawley rats will affect motivation to consume alcohol and if sweet solutions will counteract the effects of stress. Sprague-Dawley rats either received water (Control group), or corticosterone 50 µg/ml (CORT groups) in the home cage for 4 weeks. Approximately 2 hours after dark onset, CORT rats were given access to 4 ml of water (Cort H2O), 30% w/v sucrose (CORT Suc), or 11% v/v high-fructose corn syrup (CORT HFCS) for 15 minutes which was intended to expose the rats to the sweet tastes without substantial post-ingestive effects of solution consumption. Following the home-cage access, rat pressed levers for 10% w/v alcohol on 20'FR3 sessions. Sensitivity to stress was tested via pharmacological stressor yohimbine as rats were given a pretreatment injection of 0.625 mg/kg yohimbine. Motivation for alcohol was tested after 5 days of abstinence (alcohol deprivation effect or ADE) and during a session with increasing response requirement on a progressive ratio (PR test). Anxiety was tested using an open field test (OFT). Results indicated that there were no differences in corticosterone consumption across groups. CORT HFCS was the only group to show higher average alcohol responding (62.2 responses) and intake (0.89 g/kg) compared to the control group. Although the main effects of yohimbine on alcohol responding were not significant, a step-wise change in sensitivity to yohimbine has shown such that the control group responding increased by 201% which was nearly double that of CORT HFCS, which increased by only 98%. On the day of ADE test, the CORT HFCS responding was less than that of Control. However, on the second day of access following alcohol deprivation, the CORT H2O responding was greater than that of Control. Responding during the PR test showed CORT HFCS responding 107% of the day prior and Control responding 159% of the day prior. However, the main effect was only trending toward significance ($p=0.09$). No differences were found in the OFT test of anxiety or locomotor behavior. In conclusion, early life stress via oral consumption of corticosterone may increase motivation to consume alcohol only under relapse-like conditions (i.e., the day after ADE test). History of access to sweet solutions such as HFCS may reduce motivation to consume alcohol under certain conditions (e.g., immediately after abstinence). The type of sweetener may play a role and the biological mechanism such as acute effect on stress mechanism should be explored further.

A26

NEURONAL ENSEMBLES IN THE NUCLEUS ACCUMBENS CONTRIBUTE TO COCAINE-PRIMED SEEKING IN FEMALE AND MALE RATS.

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Individuals with Cocaine Use Disorder experience high rates of relapse that contribute to increased morbidity and mortality. Evidence from rat models of relapse to cocaine use suggests that sparse groups of neurons (i.e., neuronal ensembles) in the nucleus accumbens (NAc) encode learned associations that drive cue-induced cocaine-seeking, a relapse-like behavior. However, the role of NAc neuronal ensembles has not been explored in drug-primed cocaine-seeking. Additionally, given that females reportedly exhibit greater cocaine-primed seeking than males, determining if neuronal ensemble activation drives this behavioral sex effect is critical. Therefore, the present study investigated the role of sex on volitional cocaine-taking, cocaine-seeking, and neuronal ensemble activation in the NAc following seeking behavior in rats. In the present study, females self-administered more infusions of cocaine than males and exhibited greater cocaine-primed seeking, which is consistent with published literature. Contrary to our hypotheses, females and males did not differ in NAc ensemble activation. While NAc ensemble activation was strongly correlated with cocaine-seeking in males, no significant correlation was present in females. These results suggest that, while necessary for cocaine-primed seeking behavior, ensemble activation in the NAc is not sufficient to drive the observed behavioral sex-effects. While circulating sex hormones and sexually dimorphic reward circuitry are implicated in cocaine-seeking, future work should investigate their interaction with relevant ensemble populations.

B17

BEHIND THE “RUNNER'S HIGH”: EFFECTS OF ACUTE EXERCISE, STRETCHING AND MEDITATION ON ANXIETY AND ENDOCANNABINOID LEVELS IN YOUTH

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Background: The beneficial effects of exercise and meditation on mental health are well established. Data in adults and animal models suggest that circulating endocannabinoids (eCBs) are elevated following acute exercise, which may explain beneficial mental health effects (e.g., lowered anxiety). However, no studies to-date have examined the impact of acute exercise or meditation on eCBs in youth. This is important because anxiety and other mental health problems typically begin during childhood and adolescence, which coincides with developmental changes in eCB signaling. This randomized controlled trial study compared effects of a 30-min (1) moderate-intensity treadmill, (2) light-intensity stretching, or (3) seated meditation session on state anxiety and circulating eCB concentrations in youth.

Methods: Data were collected from 36 youth in an ongoing study (50% female, 9-17 years) from Metro Detroit. State anxiety and eCB concentrations were measured before and after randomization into one of the three conditions: treadmill exercise (N=15), stretching (N=12) or meditation (N=9). During the single 3-4 hour study visit, youth completed the following activities: informed parent/guardian consent and youth assent, baseline anxiety and mental health questionnaires, baseline blood draw, a 30 minute exercise or meditation session, post-exercise anxiety and mental health questionnaires and a post-exercise blood draw. This study was approved by the Institutional Review Board.

Results: There was a significant decrease in anxiety scores from before to after the 30-minute session ($p<0.002$), regardless of condition. There were no significant main effects of condition, nor significant time by intervention interaction on anxiety scores ($p=0.82$). Participants exhibited higher pre-to-post concentrations of the eCB anandamide following the treadmill condition; however, these effects did not reach statistical significance ($p>0.05$).

Discussion: Our results demonstrate that acute exercise of both light and moderate intensity, as well as meditation, are associated with reductions in state anxiety in youth. Exercise and meditation may be a relatively low-cost, low-risk behavioral intervention as an addition to pharmacotherapy or psychotherapy for combatting mental health problems in youth. Although not significant, preliminary analyses suggest that moderate-intensity exercise is associated with elevations in circulating eCBs.

B18

CENTRAL AMYGDALA CORTICOTROPIN RELEASING FACTOR NEURONS PROJECT TO THE VTA TO MEDIATE INCENTIVE MOTIVATION

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Corticotropin releasing factor (CRF) is a hormone that mediates behavioral response to stress and is typically associated with distress and anxiety. The opponent process theory suggests people take drugs to alleviate withdrawal states, which are thought to occur via an increase in CRF from central amygdala (CeA) CRF neurons. However, optogenetic activation of CRF neurons in the central amygdala can also generate incentive motivation without distress. To study this paradoxical role, we first examined the ability of CeA CRF neuron activation on focusing reward choice and incentive motivation. We presented animals with the opportunity to lever press for either a sucrose or a cocaine reward, one of which is delivered with optogenetic activation of CeA CRF neurons. Furthermore, we sought to identify the underlying neural circuitry responsible for CRF-driven incentive motivation. Studies illustrate that there are CRF inputs into the VTA, and CRF microinjections or antagonism can change dopamine transmission from the VTA as well as rats' motivational behavior for reward pursuit or anxiety aversion. We have begun to anatomically and to behaviorally characterize a direct projection of CeA CRF neurons to the VTA. We find that CeA CRF activation biases reward choice and that CeA CRF neurons project to the VTA to drive incentive motivation.

B19

THE ROLE OF CENTRAL AMYGDALA CORTICOTROPIN RELEASING FACTOR NEURONS IN MOTIVATION AND ADDICTION

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Corticotropin-releasing factor (CRF) from neurons in the central amygdala (CeA) have traditionally been posited to generate distress that motivates reward seeking and relapse in addiction. However, new evidence suggests that CRF is alternatively involved in promoting incentive motivation to increase reward pursuit without requiring an aversive stress state. It is unclear what CRF circuitry underlies this incentive motivation and whether these CeA CRF neurons are generating incentive effects via CRF release or other co-released neurotransmitters. To determine whether CRF is necessary for appetitive motivation, we optogenetically stimulated CRF neurons in the CeA while administering an intraventricular CRF antagonist and assessed motivation. Furthermore, we optogenetically activated CeA CRF projections to the lateral hypothalamus (LH) to characterize their role in CRF-driven incentive motivation. Lastly, extended cocaine experience could flip the valence of CeA CRF neurons from generating incentive motivation to aversive motivation consistent with opponent process theories of addiction. To determine the effects of long-access cocaine self-administration (LgA) on CRF-driven motivation, animals underwent 21 days of cocaine self-administration followed by assessment of CRF-driven motivation to test if CRF valence switches from appetitive to aversive during drug withdrawal and following abstinence. We found that optogenetic stimulation of CeA CRF neurons drives incentive motivation that is eliminated by global CRF antagonism. Furthermore, we show preliminary data that suggest the projection of CeA CRF neurons to the LH generates incentive motivation and that activation of CeA CRF neurons remains incentive during periods of withdrawal.

B20

ROLE OF NEUROMEDIN S-EXPRESSING VENTRAL TEGMENTAL AREA NEURONS IN MORPHINE BEHAVIOR

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Opioid dependence and addiction constitute a major health and economic burden, but our limited understanding of the underlying neurobiology limits better interventions. Alteration in the activity and output of dopamine (DA) neurons in the ventral tegmental area (VTA) is known to contribute to drug effects, but the mechanisms underlying these changes remain relatively unexplored. We used TRAP to identify gene expression changes in VTA DA neurons following chronic morphine and found that Neuromedin S (NMS) is enriched in VTA DA neurons, and its expression is robustly increased by morphine. However, whether all VTA DA neurons express NMS, and their potential functional impact has yet to be determined. We hypothesize that NMS neurons represent a novel subset of VTA neurons that contribute to morphine-elicited behavior. Specifically in these studies, we hypothesize that activating and inhibiting VTA-NMS neurons will promote and inhibit morphine behaviors, respectively. To test this, adult male and female NMS-Cre mice and wild-type littermates were used. Cre-dependent viral vectors were stereotaxically injected into the VTA to allow for DREADD-mediated activation (Gq) or inhibition (Gi) of VTA-NMS neurons. Behavioral analyses were completed two weeks after surgery. Locomotor activity was assessed following saline (d1), saline + Clozapine-N-oxide (CNO, 0.3mg/kg, ip, d2-d3), and morphine (15mg/kg) + CNO (d4-d8). A morphine + CNO challenge was done 1 week following d8. Conditioned place preference (CPP) was also performed. Mice underwent a 20 min. pre-test, followed by conditioning sessions where they received vehicle + saline in the morning and CNO + morphine (0.3mg/kg and 15mg/kg, respectively) in the afternoon for 4 days. Morphine preference was assessed during a 20 min. post-test. Significant differences ($p<0.05$) were determined using a repeated-measures two-way ANOVA for locomotor behavior and paired t-tests for CPP (pre-test vs. post-test). We find that both male and female NMS-Gq mice exhibit increased morphine-induced locomotor activity compared to controls. Additionally, locomotor response to a challenge morphine + CNO injection was significantly increased in NMS-Gq mice compared to controls. NMS-Gi mice show a trend for the opposite effect, with a decreased locomotor response to a challenge morphine + CNO injection. In CPP assays, NMS-Gq mice displayed a similar morphine-CNO CPP to controls. However, NMS-Gi mice exhibited decreased morphine-CNO CPP compared to controls. Thus, manipulation of VTA-NMS neuronal activity alters morphine-elicited behaviors including locomotion, sensitization, and CPP. Future studies will determine whether VTA-NMS neuronal activity modulates other morphine behaviors. Our current data suggest that VTA-NMS neurons represent a subset of neurons that may be functionally relevant for morphine responses.

B21

MEDIATIONAL PATHWAYS AMONG SUBSTANCE USE DURATION, CONSEQUENCES, AND QUIT ATTEMPTS

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Drug addiction is conceptualized as a chronic, relapsing brain disease characterized by compulsive drug use despite adverse consequences. Insofar as they are aversive, consequences can motivate abstinence (quit attempt). Alternatively, chronological aging effects, i.e., cognitive maturation (enhanced decision-making and inhibitory control), may facilitate greater control over one's drug use and thus, manifest as a quit attempt, unrelated drug use consequences. Here, we evaluated two mediational models among large cohorts of cocaine- and opioid-using individuals. Specifically, for each cohort, we tested whether substance-specific drug-use quit attempts were more strongly related to substance-specific adverse consequences vs. chronological age as a function of duration of substance use.

Current cocaine-using (n=175; urinalysis-verified) and current opioid-using individuals (n=168; urinalysis-verified) were recruited locally. Substance-specific drug use consequences, age at first use, and number of quit attempts were quantified via retrospective self-report. Using PROCESS in SPSS v27, mediation models tested whether substance-specific drug use consequences (vs. chronological age) mediated the relationship between duration of drug use (predictor) and number of drug quit attempts (dependent variable; indirect effects estimated using 5000-iteration bootstrapping technique) for each drug cohort.

Current cocaine users were 44.3±8.6 years old and reported 17.3±8.6 years of cocaine use, 12.4±9.1 past-month cocaine uses, 11.8±23.2 cocaine quit attempts, and 4.1±4.0 cocaine use-related consequences. Among cocaine users, cocaine use consequences mediated the relationship between cocaine use duration and cocaine quit attempts, with and without chronological age entered as a covariate ($R2 = 0.30$; $p < .001$ [full mediation] and $R2 = 0.29$; $p < .001$ [partial mediation], respectively). Conversely, age did not mediate the relationship between cocaine use duration and quit attempts.

Among the heroin-using cohort, subjects were 41.5±11.1 years old and reported 27.1±8.5 years of heroin use, 27.2±6.3 past-month heroin uses, 9.4±19.2 heroin quit attempts, and 7.6±4.5 heroin use-related consequences. Heroin use consequences fully mediated the relationship between heroin use duration and heroin quit attempts, controlling for current age ($R2 = 0.17$, $p < .001$; non-significant without age as covariate), whereas age did not mediate the relationship between heroin use duration and heroin quit attempts.

The present findings indicate that drug use consequences mediated the relationship between use duration and quit attempts in both long-term cocaine and heroin users, whereas age did not. There was a strong relationship between consequences and quit attempts highlighting the motivational influence of negative reinforcement, which was dissociated from cognitive maturation, as indexed by chronological age, in this study. Our findings are consistent with the robust literature describing neurobiological deficits in decision-making and inhibitory control among persons with addiction, and suggest that quantification of drug use-related consequences during clinical intake may be a valuable metric for determining readiness to quit.

B22

DISSOCIATING ‘LIKING’ AND ‘WANTING’ WITHIN THE VENTRAL PALLIDUM: AN OPTOGENETIC STUDY

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Previous research has identified the ventral pallidum (VP) as a key region in the brain systems that modulate ‘liking’ and ‘wanting’ for reward (Castro et al., 2015; Root et al., 2015; Smith et al., 2009). Studies using neurochemical microinjections demonstrate that the caudal VP contains a hedonic hotspot that mediates ‘liking’ and that ‘wanting’ is modulated by the rostral and caudal extents of the VP (Ho & Berridge, 2013; Smith & Berridge, 2005). This project investigated whether laser stimulation within the caudal VP increased ‘liking’ behavior and if ‘wanting’ was mediated by both the anterior and posterior VP. We found some evidence that
laser activations enhanced ‘wanting’ in ChR2 VP rats during studies of self-stimulation, but hedonic ‘liking’ behavior and tests of food intake were unaltered by the same ChR2 activations. Our findings offer guidance for future optogenetic studies within the VP and can provide a broader understanding of the neural circuits of reward that may become dysregulated in several eating disorders, depression, and addiction.

B23

CHARACTERIZATION OF OXYTOCIN NEURONS AFFECTING SOCIAL BEHAVIORS

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Exposure to psychosocial stress can contribute to development of multiple mood-related disorders including major depressive disorder (MDD), anxiety, and post-traumatic disorders. MDD is driven by complex genetic and environmental factors, but the biological etiology of MDD remains unknown. About half of MDD patients do not respond fully to existing treatments, and therefore there is a critical need for further understanding MDD etiology and development of new therapeutic targets. Additionally, MDD disproportionally affects women, with the female prevalence rate almost double that of men, but the biological basis of this sex difference is not fully understood. Chronic social defeat stress induces behaviors in mice that are relevant to disorders like MDD, including increased social vigilance and decreased social interaction. Oxytocin (OT) is a well-known modulator of social behaviors, and the bed nucleus of the stria terminalis (BNST) and paraventricular nucleus (PVN) of the hypothalamus are important coordinators of social behavior and anxiety. Our previous work demonstrates that BNST-OT neurons reduce social approach and increase social vigilance behavior, and OT knockdown in the BNST blocked stress-induced changes in social approach and vigilance behaviors (Duque-Wilckens et al., 2020). However, the physiological properties of these OT neurons and how they are affected by stress, as well as the neural circuits upstream and downstream of these OT neurons, remain unclear. We used ex vivo whole cell slice electrophysiology on OT-cre::L-10 GFP mice to examine the physiological properties of unstressed male and female adult mice. BNST- and PVN-OT neurons had increased sEPSC frequency, but not amplitude, compared to non-OT neurons in the same region or slice (cortex), indicating an extremely high excitatory drive on these neurons. No sex differences were found in either OT neuron population. Current studies are determining 1) the effects of stress on these neuronal properties; 2) the spine density of these BNST- and PVN-OT neurons through cell-filling; 3) other neurotransmitters associated with the OT neurons (i.e., glutamate, GABA, etc.); and 4) the source(s) of their glutamatergic inputs via viral tracing to uncover the circuit(s) that may contribute to OT neuron effects on chronic stress responses.

B24

THE ROLE OF NUCLEUS ACCUMBENS CORTICOTROPIN-RELEASING FACTOR IN INCENTIVE MOTIVATION

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Corticotropin-releasing factor (CRF) is widely understood to be a stress hormone associated with negative affect and distress, though some CRF systems have been shown to generate positive affect and incentive motivation. For example, optogenetic activation of CRF neurons within the nucleus accumbens (NAc) generates focused and enhanced motivation for rewards. However, in addition to the CRF peptide, CRF neurons co-release other neurotransmitters (GABA, somatostatin, dynorphin, neurotensin). To understand whether the incentive role of NAc CRF neurons is mediated specifically by the CRF peptide, Crh-cre rats received an i.c.v. injection of either a vehicle control or the CRF receptor antagonist D-Phe-CRF prior to self-stimulation and two-choice sucrose tasks. We found that antagonism of CRF receptors attenuates incentive motivation driven by optogenetic stimulation of NAc CRF neurons. This finding identifies a new role for CRF at the intersection of stress and motivation that may have implications for understanding addiction.

Keywords: stress, incentive motivation, optogenetics, antagonism, nucleus accumbens, addiction, opponent process, corticotropin-releasing-factor, dopamine

B25

CONSUMPTION OF OREO COOKIES DOES NOT LEAD TO BEHAVIORAL SENSITIZATION OR CHANGE FOS EXPRESSION IN THE NUCLEUS ACCUMBENS OF MALE AND FEMALE RATS

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Consumption of a high-fat high-sugar diet is detrimental to behavioral and neurocognitive outcomes (Reichelt et al., 2019), and foods high in fat and sugar, such as Oreo cookies, cause alterations in behavior and brain function that are comparable with those caused by drugs of abuse. Behavioral sensitization is a rodent model used to quantify phenotypic locomotor responses to substances of abuse and the neurobiological mechanisms underlying such responses. We used this model to evaluate the extent of similarity with regard to neurobehavioral responses between a high fat, high sugar food, such as Oreos, and of drugs of abuse. We hypothesized greater consumption of Oreos over time would lead to behavioral sensitization and an increase of Fos positive cells, a marker of neuronal activity, in the reward center of the brain (i.e., nucleus accumbens).

To test this, male and female Sprague-Dawley rats were divided into two groups and given unsalted rice cakes or Oreos for 30 minutes once daily for 10 days. Consumption was measured in grams eaten and this value was used to derive kilocalories consumed. Distance traveled was measured to assess locomotor activity and behavioral sensitization following repeated reward exposure. After a 21-day period without access to Oreos or rice cakes, rats underwent a challenge day. Each group was divided in two again and were provided with unsalted rice cakes or Oreos creating a 2(sex) x 2(Oreo/rice cake) x 2(challenge Oreo/rice cake) design. Consumption and distance traveled were measured. After challenge testing, the rats were euthanized and brains were extracted to quantify the number of Fos positive cells in nucleus accumbens with immunohistochemistry and fluorescence microscopy.

Analysis showed no differences in distance traveled during the 10-day period or on the challenge day among any group, including sex. But, during the 10-day period, the Oreo groups consumed significantly more kilocalories for both sexes. Furthermore, the groups that received Oreos during testing and on the challenge day consumed significantly more kilocalories than the group that received rice cakes during testing and on the challenge day suggesting a sensitization of consumption behavior. The results of the Fos labeling in the nucleus accumbens, however, did not show significant differences among groups.

These findings indicate that high fat, high sugar foods may potentiate sensitization of consumption behavior, but that these foods do not produce the locomotor-based behavioral sensitization observed with drugs of abuse. The expected Fos activation in the brain reward hub was also not observed after consumption of high fat, high-sugar foods, which may indicate that mechanisms underlying consumption of and addiction to high-fat, high-sugar foods follow unique mechanisms that are better revealed using other rodent models and looking at other brain regions involved in response to addictive substance.

B26

INVESTIGATING THE ROLE OF GCG IN THE VENTRAL TEGEMENTAL AREA IN MORPHINE BEHAVIORS

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Although opioid dependence and addiction continue to constitute a major health and economic burden, our limited understanding of the underlying neurobiology limits better diagnostics and interventions. Dysregulation of the mesocorticolimbic reward circuit is acknowledged to contribute to various aspects of drug addiction, with alteration in the activity and output of dopamine (DA) neurons in the ventral tegmental area (VTA) known to contribute to the rewarding aspects of drug use. However, the molecular mechanisms underlying these changes in VTA DA function remain relatively unexplored. Thus, we used translating ribosome affinity purification (TRAP) to identify gene expression changes in mice that specifically occur in VTA DA neurons following chronic morphine exposure. We found that expression of several neuropeptides not traditionally described in the VTA are robustly induced by morphine exposure. Glucagon-like peptide-1 (GCG) was of particular interest as it was enriched in VTA DA neurons and its expression was robustly increased following chronic morphine exposure. These data support increased GCG expression in the VTA following multiple types of opioid exposure and form a strong premise for studying GCG function. Thus, we hypothesize that activity of VTA GCG neurons contributes to morphine-elicited behaviors. To test this, we have begun to characterize the expression and functional impact of VTA DA neurons that co-express GCG using GCG-Cre mice and Cre-dependent viral vectors. Specifically, we are using DREADDs, designer receptors exclusively activated by designer drugs, to selectively activate or inhibit VTA-GCG neurons. We stereotaxically injected the excitatory DREADD hM3Dq (AAV-DIO-hM3Dq-mCherry) into the VTA of male and female wild-type and GCG-Cre mice and found that acute activation of VTA-GCG neurons via i.p. injection of clozapine-N-oxide (CNO, 0.3 mg/kg) does not affect general locomotor activity or elicit conditioned place preference or aversion (n = 5,9). We are now assessing whether activation of VTA-GCG neurons alters morphine-elicited behaviors (conditioned place preference, locomotor sensitization). Our preliminary data suggest there may be a decrease in morphine-induced locomotion and morphine CPP in animals whose VTA-GCG neurons were activated. Studies are currently underway to assess these behaviors in a second cohort of mice. Together, these studies are expected to set the stage for future work investigating the role of specific VTA-DA GCG circuits, their activity during behavior, and their potential as targets for therapeutic intervention.

B27

ENDOCANNABINOIDS AND STRESS-RELATED DISORDERS: A SYSTEMATIC REVIEW OF BASAL LEVELS AND RESPONSES TO ACUTE PSYCHOSOCIAL STRESS

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Background: Dysregulation of the endocannabinoid (eCB) system is implicated in stress-related neuropsychiatric disorders (e.g., anxiety, depression, PTSD). Despite this, no systematic review of the literature has been published that illuminates the role of eCBs—specifically anandamide (AEA) and 2-Arachidonoylglycerol (2-AG)—at rest or in response to acute psychosocial stress in individuals with and without stress-related disorders (SRDs). To address this gap, we systematically reviewed the literature on (1) effects of acute psychosocial stress on eCB levels in healthy individuals, (2) basal eCB concentrations among individuals with and without SRDs, and (3) differential eCB responses to acute psychosocial stress in healthy and SRD groups.

Methods: A review of the MEDLINE (PubMed) database was performed for original articles examining circulating eCB levels (i.e., plasma, serum) both at rest and in response to acute psychosocial stress (e.g., Trier Social Stress Test, cold pressor) in individuals with and without SRDs. A total of 319, 311, and 107 articles were screened for inclusion in reviews 1, 2, and 3, respectively.

Results: In review 1, AEA results varied, 6 (3 statistically significant) of the 16 included studies reported an increase, 4 reported a decrease, 3 reported mixed results, and 3 did not report AEA levels following acute psychosocial stress in healthy individuals. Findings for 2-AG were more consistent, 7 studies (2 significant) reported increased 2-AG levels; 1 reported a decrease; 2 reported mixed results; 6 did not report 2-AG concentrations. In review 2, 17 studies were included that compared basal eCB concentrations between SRD and healthy groups. Of those, 10 (3 significant) and 9 (2 significant) studies reported higher basal AEA and 2-AG levels in the SRD group as compared to the healthy group, respectively, whereas 7 (2 significant) and 6 (2 significant) studies reported lower basal AEA and 2-AG levels. One study found mixed 2-AG results, and the remaining study did not report 2-AG concentrations. In review 3, 1 of the 4 included studies reported a time x group interaction in 2-AG following acute psychosocial stress, such that the healthy group exhibited an increase, and the SRD group exhibited a decrease. Conversely, 4 and 3 studies did not report differential eCB responses between groups for AEA and 2-AG, respectively.

Conclusion: This systematic review revealed inconsistent findings in eCB levels at rest and in response to acute psychosocial stress, in those with and without SRDs. Additionally, most of the included studies involving SRDs focused on PTSD, underscoring the need for exploration of other diagnoses. Moreover, methods and information on potential covariates (e.g., cannabis use, medication use) varied widely across studies. This review emphasizes the need for more studies on the role of the eCB system in SRDs.

A27

THE SNX17-RETRIEVER ENDOMEMBRANE RECYCLING PATHWAY IS A KEY REGULATOR OF SYNAPTIC FUNCTION AND PLASTICITY IN HIPPOCAMPAL NEURONS

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The insertion and removal of integral membrane proteins is a key mechanism for the regulation of synaptic function. Once surface proteins are internalized, they can either be routed to lysosomes for degradation or can be recycled back to the cell surface. Two recycling protein complexes - the SNX27-Retromer complex and the recently discovered SNX17-Retriever complex - are the main drivers in recycling internalized cargoes in non-neuronal cells. In neurons, the SNX27-Retromer pathway has been shown to regulate surface expression of AMPA-type glutamate receptors (AMPARs) during long-term potentiation (LTP), but almost nothing is known regarding the role of the SNX17-Retriever pathway at synapses. Here, using cultured hippocampal neurons, we demonstrate that the SNX17-Retriever pathway localizes to both synaptic and extra-synaptic sites and that RNAi-mediated disruption of this pathway leads to the functional and structural loss of excitatory synapses. Moreover, we find that synaptic stimulation leads to the recruitment of SNX17 to synaptic sites in a manner that depends on Ca2+ influx through NMDARs, activation of CaMKII, and Retriever complex binding. Knockdown of either SNX17 or the Retriever subunit DSCR3 prevents structural plasticity of dendritic spines during LTP. Finally, this loss of structural plasticity is associated with altered trafficking of the cell adhesion molecule β1 Integrin, which is a SNX17 cargo in non-neuronal cells and as we show, in neurons as well. Preliminary studies suggest that SNX27 and SNX17 sort distinct cargos in neurons, suggesting that these two recycling pathways each play important, but unique, roles at synaptic sites.

A28

THE COORDINATION OF VOLTAGE-GATED SODIUM CHANNELS VIA ANKYRIN PROTEIN INTERACTIONS

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Voltage-gated sodium channels (NaVs) are essential regulators of neuronal excitability, making the dysfunction of NaVs a serious public health concern. Genetic variants in SCN2A and SCN8A, which encode the neuronal sodium channels NaV1.2 and NaV1.6, respectively, have been identified in several human patient cohorts of neurodevelopmental disorders, including autism spectrum disorder (ASD) and epileptic encephalopathy (EE). The proper localization of NaVs is dependent on their interactions with ankyrins, a family of intracellular scaffolding proteins that link essential membrane-bound proteins to the underlying cytoskeleton. Our lab and others have established ankyrin-G, encoded by ANK3, as the master organizer of the axon initial segment (AIS), a key site of neuronal excitability. Ankyrin-G scaffolds proteins to the AIS, including NaV1.2 and NaV1.6. Our lab recently identified a critical interaction between NaV1.2 and ankyrin-B, encoded by ANK2, in mature neocortical pyramidal cell dendrites, where NaV1.2 regulates dendritic excitability. Previous studies have identified the key residues required for the binding of ankyrins and NaVs. The key residues required for the interaction between ankyrin-B and NaV1.2 are found within the ankyrin-repeats of ankyrin-B and the intracellular loop between domains II and III (II-III loop) of NaV1.2. These residues are conserved among ankyrin-B and ankyrin-G, and NaV1.2 and NaV1.6. Despite this conservation, ankyrins and NaVs have distinct neuronal localization, suggesting that regions outside of the required residues play a role in the coordination of NaVs. However, it remains unknown which amino acid sequences determine binding affinity between ankyrins and NaVs to mediate differential ankyrin-dependent coordination of NaVs.

Our preliminary data indicate that mutations near the ankyrin/NaV binding interface affect the binding affinity between ankyrin-B and NaV1.2. The effects of these mutations on the binding affinity between NaV1.2 and ankyrin-G, however, have not been characterized. Furthermore, potential interactions between ankyrin-B and NaV1.6 have not been studied. Altered binding affinities could explain differences in the localization and function of these proteins. In addition, limitations in immunocytochemistry techniques have prevented a close study of NaV1.6 localization outside the AIS. These results would provide critical information regarding the ankyrin-dependent coordination of NaVs and ultimately help us determine how dysfunction of ankyrins and NaVs contribute to the etiology underlying neurodevelopmental disorders.

A29

THE PERSISTENT AND MULTIDIMENSIONAL MICROGLIAL RESPONSE TO PATHOLOGICAL ALPHA-SYNUCLEIN AGGREGATION

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It remains unclear whether inflammation, triggered by either alpha-synuclein (α-syn) aggregation and/or degeneration, contributes to progression of Parkinson's disease (PD). The distinct aggregation and degenerative phases of the α-syn preformed fibril (PFF) model provides a platform to investigate α-syn inclusion-associated immunogenicity. Previously we have observed a localized subpopulation of reactive microglia surrounding phosphorylated α-syn (pSyn) inclusions in the substantia nigra pars compacta (SNpc) following PFF injection. Specifically, microglia immediately adjacent to pSyn inclusions increase soma size and major-histocompatibility complex-II (MHC-II) expression, this microglial response is proportional to the magnitude of pSyn accumulation and precedes SNpc degeneration. Understanding the potential role and inflammatory phenotype of a-syn aggregate associated microglia (a-SAMs) could facilitate future anti-inflammatory, disease-modifying strategies for PD. Partial microglial depletion of microglia using a colony stimulating factor-1 receptor inhibitor was used to determine the role of microglia in degeneration. Despite significant microglial depletion, a-SAM MHC-II immunoreactivity and increased soma size was maintained and degeneration of SNpc neurons was unaffected. Further, widespread, extranigral MHC-IIir expression was observed with long-term partial microglial depletion. These results suggest that microglial depletion is not a promising anti-inflammatory therapeutic strategy for PD and that this approach may induce a heightened proinflammatory state in remaining microglia. Fluorescent in situ hybridization and droplet digital PCR revealed that pathological α-syn inclusions in the SNpc are associated with perturbations in immune functions related to complement, inflammasome, T cell activation, phagocytosis, and interferon gamma signaling. Specifically, Cd74, Cxcl10, Rt1-a2, Grn, Csf1r, Tyrobp, C3, C1qa, Fcer1g, Cd4, Stat1, Casp 1, Axl, Lyz2, and IL18 are significantly upregulated in microglia and pSyn inclusion-bearing SNpc. Collectively, these results demonstrate that the microglial response to pathological α-syn aggregation is persistent and multifaceted. Comprehensive understanding of the microglial response to pSyn inclusions may uncover novel therapeutic targets to identify anti-inflammatory, disease-modifying strategies for PD.

B28

EFFECTS OF CANNABIDIOL ON COMPARTMENT SPECIFIC DOPAMINE RELEASE IN THE STRIATUM

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Cannabidiol (CBD) is a non-psychoactive compound present in large amounts in Cannabis sativa, recreationally known as marijuana. Legalization of the use of marijuana contributed to the desire to know how specific substances in marijuna affect the physiology of the brain. Recently, CBD was identified as a modulator of the release of different neurotransmitters in different regions of the brain, such as GABA, glutamate, and dopamine. This behavior is attributed to CBD's interaction with the endocannabinoid system, a system known to be a homeostatic modulator. Previous studies carried out in our lab specifically examining how CBD affects dopamine neurotransmission in the dorsal striatum of Mus musculus showed a change in dopamine neurotransmission after CBD exposure, however, the direction of the change was inconsistent. Recent studies investigating neurotransmitter release have emphasized the importance of small structures of differential histochemical composition within the striatum, referred to as striosomes. Neurons within striosomes behave differently than non-patch neurons when exposed to different neurotransmitters. Measurements of dopamine neurotransmission in the dorsal striatum of Mus musculus were recorded in real time before and after exposure to CBD and categorized by striatal region to identify if there was compartment specific release of dopamine in response to CBD exposure.

B29

MARESIN 1, A DOCOSAHEXAENOIC ACID-DERIVED PRO-RESOLUTION LIPID MEDIATOR, AMELIORATES INFLAMMATION, PROMOTES NEUROPROTECTION, AND PREVENTS DISEASE PROGRESSION IN PRECLINICAL ANIMAL MODEL OF MULTIPLE SCLEROSIS

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Background: Multiple sclerosis (MS) is the most common inflammatory neurodegenerative disease in young adults, resulting in neurological defects and disability. The endogenous mechanisms for resolving inflammation are intact but become defective in patients, resulting in lack of resolution mediators and unresolved chronic inflammation. Objectives: Since docosahexaenoic acid (DHA) metabolism is impaired in MS, we hypothesize that supplementing its downstream metabolite maresin 1 (MaR1) will alleviate inflammation and demyelination in preclinical mouse model of MS; experimental allergic encephalomyelitis (EAE). Methods: EAE was induced in SJL mice, followed by intraperitoneal treatment with 300ng (200ul in PBS/mouse/daily) of MaR1 from day 6 post-disease induction. Monitoring the disease course for clinical signs up to day 70, measuring disease activity by infra-red activity monitoring system (IRAMS), recall response by ELISA, cytokine expression analysis by qPCR, western blotting, and immune profiling by flow cytometry were used to assess the effect of MaR1 treatment in EAE. The neuroprotective effect of MaR1 was also assessed using single molecule array (SIMOA), histopathology (HE and LFB), immunofluorescence (IF), and immunohistochemistry (IHC). To confirm that MaR1 mediates its effect through IL10 signalling pathway, IL10 was neutralized in EAE by anti-IL10 antibody (200ug/mouse, twice a week, ip), followed by daily treatment with MaR1 till the end of the study. Statistical analysis was done using Graph-Pad Prism. Results: Restoration of MaR1 had a protective effect on neurological deficits, prevented disease progression, and reduced disease severity in EAE by reducing immune cell infiltration (CD4+IL17+ and CD4+IFN+) into the CNS ($P<0.001$). It significantly reduced the proinflammatory cytokine IL17 ($P<0.01$) and promoted an anti-inflammatory response via IL10 and IL4 ($P<0.001$). Furthermore, it improved the pathophysiology and exerted neuroprotective effects as evidenced by lower levels of NFL ($P<0.01$) in the plasma of treated group compared to control and higher MBP expression in the brain from the MaR1 treated mice, decreased inflammatory infiltrates, and less demyelination and vacuolization in the spinal cord tissue sections of treated mice. Neutralization of IL10 abolished the protective effect of MaR1 in EAE suggesting IL10 is mediating MaR1 effect in EAE. Conclusions: Overall, MaR1 supplementation has anti-inflammatory and neuroprotective effects in preclinical animal models, implying that it could be a new therapeutic molecule in MS and other autoimmune diseases.Keywords: Inflammation, Resolution, DHA, Maresin1, MS, EAE, IL10, Therapeutics

A30

TAU INTERACTOME MAPPING USING THE BIOID2 APPROACH IDENTIFIES INTERACTIONS WITH PROTEINS ASSOCIATED WITH VARIOUS CELLULAR COMPARTMENTS

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Pathological inclusions composed of tau protein are hallmarks of neurodegenerative diseases collectively known as tauopathies, of which the most common is Alzheimer's Disease (AD). Tau is most well-known as a microtubule-associated protein involved in regulating microtubule dynamics, but accumulating evidence suggests tau is involved in many biological functions. Deciphering the tau protein interactome is critical for better understating the physiological and pathological roles of tau. This work aimed to identify tau interacting partners using the in situ protein labelling BioID2 method by creating fusion proteins between full-length human tau and BioID2 on either the N-terminus (BioID2-Tau) or C-terminus (Tau-BioID2). Utilizing this approach, we identified 280 potential interactors with Tau-BioID2 and 178 potential interactors with BioID2-Tau, of which 67 proteins were identified in both Tau-BioID2 and BioID2-Tau. Gene Ontology (GO) enrichment analysis using cellular compartment terms indicated interactions with proteins known to be found in the cytoskeleton, mitochondria, somatodendritic compartment, synaptic vesicles, and RNA-binding proteins. While GO molecular function pathways identified proteins involved in RNA binding, translation regulation, ubiquitin ligase activity, kinase binding, mitochondrial oxidoreductase, and peroxidase activity. KEGG pathway analysis identified proteins associated with neurodegenerative diseases, including AD, Parkinson's disease, Huntington's disease, and Amyotrophic lateral sclerosis. These results suggest that this approach can be applied to identify novel protein-protein interactions via an in situ labeling method that could facilitate detection of transient and/or weak interactors. Moreover, the identified proteins could help shed light on tau's growing functional roles in neurons under both physiological and pathological states helping to better understand its biological and neurodegenerative roles.

A31

SYNUCLEINOPATHY ACTIVATES THE COMPLEMENT SYSTEM AND DECREASES CD55 EXPRESSION IN NIGRAL NEURONS PRIOR TO NEURODEGENERATION.

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Parkinson's disease (PD) is characterized by loss of midbrain dopamine neurons, the accumulation of pathological alpha synuclein (a-syn) in Lewy bodies and neuroinflammation. Neuroinflammation occurs in early-stage PD patients and remains elevated through the course of the disease, suggesting it may contribute to neurodegeneration. The complement system is a division of the innate immune system that coordinates the clearance of debris, synapses, and cells in the central nervous system. Activated complement proteins label a-syn containing Lewy bodies in the PD brain. These data suggest that the complement system may mediate phagocytic removal of neurons containing pathological a-syn. However, activation of the complement system in PD and associated models has only been documented after significant neurodegeneration has occurred. Thus, it is impossible to determine if complement activation occurs in response to cell death or prior to cell death, where it may drive to neurodegeneration. We aimed to test the hypothesis that complement activation occurs in the substantia nigra pars compacta (SNc) prior to overt neurodegeneration in a model of synucleinopathy. Intra-striatal injection of recombinant a-syn pre-formed fibrils (PFFs) results in progressive aggregation of endogenous a-syn and gliosis that peaks 2 months post injection, followed by significant nigral degeneration at 6 months post injection. To determine if synucleinopathy causes complement activation prior to cell loss we used ddPCR to quantify complement transcripts representing different parts of the complement cascade. We observed significant increases in transcripts from targets of the classical (C1qa, C4b) and alternative activating pathways (CFd, Cfb), the anaphylatoxin receptors (C3aR, C5aR), the phagocytic receptor CD11b (ITGAM) and the complement regulator, C1 Inhibitor (Serping1). Surprisingly, we observed significant decreases in transcripts of the complement regulators CD55 and CD59. We next performed immunofluorescence (IF) in the SNc at the same time point to determine if the decrease in CD55 occurred in nigral neurons. CD55 immunoreactivity was decreased in nigral neurons of PFF injected rats, where neurons containing phosphorylated a-syn (pSyn) were almost completely devoid of CD55 immunoreactivity. Using the proximity ligation assay were observed interaction between a-syn and CD55 in the rat SNc, which was increased by phosphorylation of a-syn at serine 129. Finally, we performed similar analyses in postmortem human PD tissue and observed decreased CD55 in nigral neurons interaction between pSyn and CD55, which was largely absent in the SNc of control patients. Finally, we observed CD55 in the core of Lewy bodies. Taken together, these data demonstrate the synucleinopathy causes a robust activation of the complement system and a decrease in the expression of membrane bound complement regulators in nigral neurons. Importantly, these changes occur months prior to neurodegeneration in our PFF model, indicating that complement activation and regulator dysfunction may contribute to neurodegeneration in PD.

A32

DEVELOPMENTAL EXPOSURE TO THE PARKINSON'S DISEASE-ASSOCIATED ORGANOCHLORINE PESTICIDE DIELDRIN INCREASES DOPAMINE RELEASE IN THE STRIATUM IN THE A-SYNUCLEIN PRE-FORMED FIBRIL MOUSE MODEL

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Parkinson's disease (PD) is the most common movement disorder and one of the fastest-growing neurological diseases worldwide. This increase outpaces the rate of aging and is most rapid in recently industrialized areas, suggesting a role of environmental factors. Consistent with this, epidemiological studies show an association between exposure to persistent organic pollutants and an increased risk of PD. When combined with post-mortem analysis and mechanistic studies, a role for specific compounds, including the organochlorine pesticide dieldrin, emerges. In mouse models, developmental dieldrin exposure causes male-specific exacerbation of neuronal susceptibility to MPTP and synucleinopathy. Specifically, our novel two hit model combining developmental dieldrin exposure with the α-synuclein (α-syn) pre-formed fibril (PFF) model showed a male-specific exacerbation of PFF-induced increases in striatal dopamine (DA) turnover and motor deficits on the challenging beam 6 months post-PFF injection in male offspring developmentally exposed to dieldrin. Here, we hypothesized that alterations in DA handling contribute to the observed changes and assessed vesicular monoamine transporter 2 (VMAT2) function and DA release in this dieldrin/PFF two-hit model. Female C57BL/6 mice were exposed to 0.3 mg/kg dieldrin or vehicle every 3 days by feeding, starting at 8 weeks of age by feeding and continuing throughout breeding, gestation, and lactation. Male offspring from independent litters underwent unilateral, intrastriatal injections of α-syn PFFs via stereotaxic surgery at 12 weeks of age and DA handling was assess 4 months post-PFF injection via vesicular 3H-DA uptake assay and fast-scan cyclic voltammetry (FSCV). We observed no dieldrin-associated change in VMAT2 activity, but a dieldrin-induced increase in DA release by in striatal slices in PFF-injected animals. These results suggest that developmental dieldrin exposure alters the dopaminergic response to synucleinopathy-triggered toxicity and supports our hypothesis that alterations in DA handling may underly the observed exacerbation of PFF-induced deficits in motor behavior and DA turnover.

A33

THE CREATION OF A NOVEL TRANSGENIC FLY LINE TO MODULATE TAU PHOSPHORYLATION NEAR THE CALPAIN CLEAVAGE SITE

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More than 6 million Americans are affected by Alzheimer's disease (AD). AD belongs to a category of diseases known as tauopathies whose pathogenesis involves hyperphosphorylation of the microtubule-associated protein tau (MAPT). A main focus of AD research involves strategies to prevent or revert the hyperphosphorylation of tau that leads to neuronal cell loss. In general, increased tau phosphorylation correlates with enhanced tau toxicity, but specifically, the mechanisms driving neuronal cell death are unclear. We hypothesize that phosphorylation of tau near a critical proteolytic cleavage site may be responsible for modulating the production of a toxic tau fragment that has been implicated in human disease. The cysteine protease calpain cleaves tau at lysine 44 (K44) and arginine 230 (R230) to liberate the toxic 17kD tau fragment. Using the tauopathy model developed in the common fruit fly, Drosophila melanogaster, we use the rough eye phenotype to assess photoreceptor neurodegeneration as a means to gauge tau toxicity in vivo. Given the powerful tools available in flies, we can modify phosphorylation near the R230 cleavage site by (1) ectopically expressing known tau kinases and phosphatases that target threonine 231 and serine 235; and (2) expressing mutant forms of human tau in which key phosphorylation sites are mutated to alanine (to prevent phosphorylation) or glutamic acid (to mimic phosphorylation). We expect that efforts to increase phosphorylation near the R230 cleavage site will amplify tau toxicity, as demonstrated by enhancement of the tau rough eye phenotype, while strategies that reduce or prevent phosphorylation will suppress the tau rough eye. The specific aim of this project was to create a transgenic fly line expressing a dominant-negative form of protein phosphatase 2A (PP2A) together with several forms of wild-type and mutant tau. The creation of this line is the end result of a multigenerational mating scheme involving transgenes on multiple chromosomes. I successfully created the stable stock of BlL/CyO; wdbDN1/Ly which will be crossed to tau-expressing flies to look for modification of the tau rough eye phenotype. The potential impact of this research is to provide treatment strategies to help Alzheimer's disease patients by illuminating novel mechanisms controlling tau toxicity.

A34

PATHOGENIC TAU MUTANTS ACTIVATE P38 MAPK AND DISRUPT FAST AXONAL TRANSPORT

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Alzheimer's disease and related dementias are characterized by neuronal and axonal degeneration that may be caused by disruption of microtubule-based fast axonal transport (FAT). Pathological forms of tau, including tau aggregates as well as some phosphorylated and/or mutant monomeric forms of the protein, can disrupt bidirectional FAT in mammalian primary neuron models. We previously demonstrated that pathological forms of tau act on anterograde transport through activation of a protein phosphatase 1 (PP1)-mediated signaling pathway that alters kinesin behavior. However, the mechanisms mediating the effects on retrograde transport, involving the cytoplasmic dynein motor complex, are not yet known. We sought to identify mechanisms by which pathological tau forms alter retrograde FAT. We used primary hippocampal neurons from tau knockout mice to the mechanisms by which pathogenic tau (FTLD-tau mutants) affect FAT. Using lentiviral-based expression of tau in the neurons we identified tau's effects on the activity levels of kinases known to modulate transport. Multiple pathogenic forms of tau induced a significant increase in levels of active p38 MAPK, a kinase linked to disease-associated FAT disruptions. We then transfected the primary neurons and measured live-cell axonal transport of fluorescent-tagged synaptophysin and Rab6 cargo proteins. Expressing pathogenic tau resulted in increased cargo pause frequency using both cargo proteins indicating abnormal transport. These tau mutants disrupt normal anterograde and retrograde FAT in primary neurons and provide a model system that is being used in ongoing experiments to examine the role of p38 kinase in mechanisms of the tau-induced toxic effect.

A35

CHEMOTAXIS OF PARENCHYMAL MICROGLIA FOLLOWING THE DEATH OF INNER RETINAL NEURONS INDUCED BY INTRAVITREAL INJECTION OF NMDA IN ZEBRAFISH

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Injury to central nervous system tissues elicits cell death, inflammation, and chemotaxis of microglia, the innate immune cells of the central nervous system. In this study, we used the zebrafish microglia reporter line, Tg(mpeg:eGFP), and immunocytochemistry to examine the response of retinal microglia in response to the selective death of inner retinal neurons following intraocular injections of N-methyl-D-aspartate (NMDA). Zebrafish eyes were injected with PBS or NMDA and immuno-stained with the antibody, HuC/D, which labels amacrine and ganglion cells, and 4C4, which labels microglia, to assess the extent of cell death and the response of microglia, respectively.

At 1 day post-lesion, HuC/D staining reveals decreases in the number of inner retinal neurons following injection of NMDA as compared to PBS. In PBS-injected retinas, microglia were observed in the subretinal space, among the cell bodies of the RPE, outer plexiform layer, inner plexiform layer, and the retinal ganglion cell layer. Microglia in control retinas displayed ramified morphologies, indicating they were not activated as no injury was expected nor perceived. In contrast, microglia in NMDA-injected retinas were present among inner retinal neurons, and displayed ameboid morphologies, indicating their activation in response to neuronal injury. Almost no microglia were observed in the outer plexiform layer, suggesting these cells migrated into the inner retina. In contrast, the prevalence, location, and morphology of microglia in the subretinal space did not differ between control and experimental retinas. This study confirms the selective death of inner retinal neurons following NMDA injection and establishes the response of microglia to this damage.

A36

THE EFFECT OF SUBSTRATE STIFFNESS ON HUMAN SCHWANN CELL ELONGATION, MIGRATION, AND PROLIFERATION

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Damaged peripheral nerves have the capacity to regenerate and re-innervate, however, depending on the severity of the PNI, this process can take weeks to years. Schwann cells (SC) are vital to peripheral nerve regeneration, however, the influence of biomaterials on their behavior is not well characterized. This study will examine the effect that substrate stiffness has on SC elongation, migration, and proliferation. Mechanical properties of hyaluronic acid (HA) were altered by the degree of methacrylate substitution as previously described [1] with low modified (LMOD) indicating 30% substitution and high modified (HMOD) indicating 60% substitution. Methacrylated HA (MeHA) was electrospun into nanofibers as previously described [2]. Tensile testing was conducted on the nanofibers in a dry as spun and hydrated state. Timelapse microscopy was used to observe the SCs (ipn 02.8) for 8 hours. Images of the cells were captured every 10 minutes. Cell pathway data was obtained using ImageJ. Cell motility coefficients and persistence times were quantified using the random walk model. Cell proliferation was tracked over 48 hours using the alamarBlue assay. Cell aspect ratio (AR) was quantified using ImageJ. Statistical significance of data was determined using t-tests.

The Young's modulus (± SD) obtained from the tensile test indicates that the HMOD MeHA is the stiffer material (Dry: 132.30 ± 26.78 MPa, Hydrated: 5.56 ± 2.85 MPa) compared to the LMOD MeHA (Dry: 96.37 ± 26.94 MPa, Hydrated: 1.73 ± 0.87 MPa). Cell motility coefficient and cell persistence time values (± SD) were higher in SCs on HMOD MeHA fibers (55.63 ± 52.03 μm2/min, 10.96 ± 6.08 min) compared to LMOD MeHA fibers (12.09 ± 10.27 μm2/min, 10.96 ± 6.08 min) indicating a greater tendency for movement with less directional changes on the stiffer substrate. Cell aspect ratio (AR) (± SD) was greater in the stiffer substrate (HMOD: 2.67 ± 1.01 μm, LMOD: 1.35 ± 0.28 μm) indicating greater elongation. Substrate stiffness also appeared to affect SC proliferation (HMOD: 18,901 ± 10,145 cells, LMOD: 13,297 ± 3,754 cells, at 48 hours). The Young's Modulus, cell motility coefficient, persistence time, and cell AR were found to be statistically significant ($p<0.05$).

Stiffer substrates have been linked to increased SC elongation, causing upregulation in pro-regenerative markers such as EGR1 [3] and the release of growth factors such as TGFβ1[4] which regulate SC migration and growth [4,5]. These results suggest that stiffer substrates may be more suitable for nerve-regeneration applications by directing SCs towards a pro-regenerative phenotype.

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A37

IDENTIFICATION OF THE EARLY MICROGLIA TRANSCRIPTOMIC RESPONSE TO ALPHA-SYNUCLEIN INCLUSION FORMATION IN THE SUBSTANTIA NIGRA FOLLOWING PREFORMED FIBRIL INJECTION

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Increasing evidence suggests that chronic inflammation may contribute to disease progression in Parkinson's disease (PD). Lewy body deposition in PD tissue is correlated with microglial reactivity, specifically upregulation of major histocompatibility complex class II (MHC-II). In the rat alpha-synuclein preformed fibril (PFF) model we similarly observe a positive association between phosphorylated alpha-synuclein (pSyn) inclusion accumulation and MHC-II expression in the substantia nigra (SN). RNA-sequencing in the SN of PFF model rats at the peak of pSyn accumulation and MHC-II expression (2 months) revealed immune effector processes to be the most enriched pathway, including increased expression of Cd74, which mediates assembly and subcellular trafficking of MHC-II. However, studies examining the microglial transcriptome support that concept that microglial phenotypes are disease stage-specific, with at least one report in an amyloid beta model suggesting microglial MHC-II expression defines a late response of microglia to disease pathology. The purpose of the present study is to evaluate whether the microglial transcriptomic response to early pSyn formation in the SN (1 month post PFF) is distinctive from that we have previously observed during the later, established peak of pSyn accumulation (2 months post PFF). Male TH-EGFP rats received two intrastriatal injections of either mouse α-syn PFFs, mouse α-syn monomer or vehicle and were euthanized via saline perfusion 1 month after surgery. Ipsilateral SN tissue was punched from frozen brains and nuclei suspensions prepared for single nuclei RNA-sequencing. Transcripts will be clustered together using Seurat, allowing for direct comparisons of the microglial-specific transcriptome between the PFF, monomer and PBS control rats, and other SN cell types. Transcripts with an FDR corrected p value < 0.05 will be considered differentially expressed. Results will be compared to microglial-associated transcripts upregulated in our existing 2-month RNA-Seq dataset. Future studies will include validation of a subset of identified transcripts within microglia 1 and 2 months following PFF injection using in situ hybridization. Results from this study will determine whether the microglial transcriptomic response to early vs. late pSyn inclusions is temporally distinctive.

A38

TARGETED CIRCUIT MANIPULATION FOR AMELIORATING HUNTINGTON'S DISEASE PATHOGENESIS

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Almost 30 years after identifying the genetic mutation underlying Huntington's disease (HD), treatments remain limited to managing late-stage symptoms of motoric, psychiatric, and cognitive deficits. Findings from patients and mouse models of HD point to pre-symptomatic imbalances in neuronal circuit activity, well before any overt symptoms are observed. Our central hypothesis is that manipulating the firing activity within selected microcircuits before the onset of symptoms by chemogenetic inhibition and/or excitation of key target populations will slow HD disease progression. A crucial early event in HD is the pathological increase in the overall excitatory output from cortex onto striatum. The enhanced excitability of cortical pyramidal neurons (CPNs) in pre-symptomatic HD is one key target for correctional intervention. The window before the onset of symptoms presents an opportunity to inhibit the firing rate of CPNs projecting to the striatum with the prospect of preventing or slowing disease progression. For manipulation of neuronal activity, we utilized bioluminescent optogenetics (BL-OG) that employs light-emitting luciferases to activate light-sensing opsins. We are testing the effects of circuit manipulation on preventing or delaying behavioral deficits in the R6/2 transgenic mouse model of HD. To selectively target CPNs projecting to the striatum, an AAV vector carrying a Cre-inducible inhibitory LMO (AAV-CamKIIa-DIO-NCS3-hGtACR1) was injected into the cortex of 3-week-old mice, while a retrogradely transported Cre-recombinase (AAVrg-hSyn-Cre-P2A-dTomato) was injected into the striatum. Two weeks later, luciferin or vehicle were administered once every other day for 2 weeks to decrease CPN firing. Rotarod, open field, and CatWalk were used to assess motor coordination, exploratory behavior, and gait function. We assessed cognitive behavior through water T-maze, novel object recognition test, and passive avoidance test. Our studies will contribute to understanding how microcircuit manipulation influences motor and cognitive behavior in HD and will drive translational progress toward novel therapeutic purposes.

A39

INFLAMMATORY STRESS CONTRIBUTES TO TAU PATHOLOGY IN THE PS19 MOUSE MODEL OF ALZHEIMER'S DISEASE

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Inflammation is a critical contributing factor during Alzheimer's disease (AD) onset and progression. However, details highlighting the specific contributions of the pro-inflammatory state present in AD remains unclear. Evidence suggests that the timing, magnitude, and type of inflammatory response all affect pathophysiological hallmarks of AD—including amyloid-β plaques, tau neurofibrillary tangles, synaptic dysfunction, and neuronal loss. The present study examined the relationship between chronic inflammatory stress induced via intraperitoneal injections of infection mimetics starting after the prodromal phase of pathological tau formation in the PS19 mouse model of AD. Mice injected with infection mimetics showed significantly elevated pathological tau formation, based on immunohistochemical analysis of tissue. While both male and female PS19 mice displayed greater pathological tau burden (irrespective of treatment group), female mice showed significantly greater pathological tau burden compared to male mice. However, total tau was not significantly different between groups. Mice receiving infection mimetics also showed a significantly greater amount of activated astrocytes compared to mice receiving vehicle (Ringers solution). These results suggest that inflammatory stress can contribute to pathological markers of AD.

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A40

USE OF SURFACE MODIFIED GENERATION 4 PAMAM DENDRIMER NANOMOLECULES TO DELIVER NEUROPROTECTIVE HORMONE, PROGESTERONE TO ISCHEMIC STROKE INDUCED RATS

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A cerebrovascular accident (CVA) is the interruption of blood flow to the brain that can lead to damage to the brain. CVAs affect hundreds of thousands of people each year in the United States. Therefore, prompt treatment and reducing complications of CVAs is timely and necessary. However, there are very few FDA approved drugs for use in stroke patients some examples (tPa – time sensitive with short time window). Previous studies have established progesterone as a neuroprotective hormone, but further studies are required in order to better deliver progesterone across the blood brain barrier. In this study, we investigated the effects on motor function in rats following progesterone treatment delivered using G4 PAMAM dendrimers used as the delivery vehicle. The right middle cerebral artery (MCA) was occluded in male and female Sprague Dawley rats for 60 minutes in order to induce a right MCA stroke. One week following the stroke induction, the rats received 10 intraperitoneal injections of either 8mg/kg of progesterone-dendrimer treatment, dendrimer only, or HBSS solution each week every other day for 5 weeks. Three motor tests were used in order to determine the effectiveness of the treatment including the ladder test, the cylinder test, and neuroscoring. Preliminary results from the ladder test showed motor improvements in weeks 3 through 5 in both the progesterone-dendrimer treatment group and dendrimer only group compared with the HBSS group. Initial results from the cylinder test demonstrated a difference between dendrimer only treated stroke rats compared to HBSS treated stroke rats. Preliminary results from the neuroscoring data show both motor improvement and a reduction in the time taken for the stroke-induced rats to recover from the infarct in the group that received progesterone-dendrimer treatment compared to the groups that received HBSS and dendrimer only. Ultimately, it was observed that the dendrimer-progesterone treatment demonstrated effects in terms of improving motor function in rats following middle cerebral artery occluded (MCAo) stroke. Additionally, our results show that the dendrimer-progesterone complex is able to cross the blood brain barrier in order to exert a physiologic affect in MCAo rats. The data suggests that the dendrimer-progesterone delivery system is a promising and effective system in order to deliver progesterone treatment intraperitoneally in occluded MCAo rat models.

A41

DISEASE MODIFYING POTENTIAL OF THIRD GENERATION ROCK INHIBITOR KL-00974 IN SYNUCLEINOPATHY MODELS OF PARKINSON'S DISEASE

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Microglial activation is associated with Lewy Body deposition in Parkinson's disease (PD) and rodent models of synucleinopathy and the chronic proinflammatory environment may contribute to neurodegeneration. Microglial migration, phagocytosis and release of proinflammatory cytokines are mediated by Rho-associated protein kinase (ROCK) activity. The third generation ROCK inhibitor KL-00974 is a more selective, potent and brain penetrant than classical ROCK inhibitors (e.g. fasudil). In the present study we evaluated the anti-inflammatory and neuroprotective potential of KL-00974 in both the alpha-synuclein adenoassociated viral (AAV) vector and alpha-synuclein (a-syn) preformed fibril (PFF) model in rats. Daily oral administration of KL-00974 significantly decreased microglial immunofluorescence and significantly prevented degeneration in tyrosine hydroxylase immunoreactive (THir) nigral neurons in the AAV a-syn overexpression model. In the a-syn PFF model, no impact of daily oral KL-00974 on accumulation of phosphorylated a-syn (pSyn) or number of major histocompatibility complex class II immunoreactive (MHC-IIir) microglia in the substantia nigra pars compacta (SNpc) are observed at 2 months. Ongoing studies will determine whether KL-00974 can impact nigrostriatal degeneration in the PFF model. Future studies will examine transcriptomic changes in the SN associated with chronic KL-00974 in the context of PFF-induced pSyn inclusions. Systematic vetting of the neuroprotective potential of KL-00974 in multiple synucleinopathy models will provide critical data to support continued development of KL-00974 as a therapeutic strategy for PD.

A42

UNIQUE OXIDATIVE STRESS SIGNATURES IN PAIN AND REWARD BRAIN REGIONS AFTER TBI IN MALE AND FEMALE MICE

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Persistent pain is experienced by over half of the ~3 million people annually affected by traumatic brain injuries (TBIs). Opioid therapies often induce paradoxical pain sensitization and addiction liability in TBI patients, underscoring the need to ascertain dynamic pain and reward alterations post-TBI to advance treatment. TBI escalates reactive oxygen species (ROS) that may increase pain and reward responding. This study aimed to quantify ROS levels using fluorometric assays in pain-(anterior cingulate cortex (ACC), thalamus, periaqueductal gray (PAG)) and reward-related (prefrontal cortex (PFC), nucleus accumbens (NAc), dorsal striatum (dStr), midbrain) brain regions over time to identify potential windows of intervention. Tissues were collected at 24 hours, 7 days, and 14 days post-injury from C57Bl/6 mice (10-12 weeks old; M/F) given moderate, closed-skull TBI or sham surgery. TBI significantly enhanced ROS levels compared to sham at 24 hours post-injury in all pain regions, except for female thalamus which showed increases at 7 days. Increases in ROS resolved by 7 days in male and female PAG, with a significant decrease from 24 hours to 14 days post-injury. Levels of ROS significantly increased from 24 hours to 14 days in male and female ACC. In the thalamus, the male group showed no significant changes between any timepoints, however, ROS remained elevated at 14 days in both male and female groups. In the reward regions, TBI significantly enhanced ROS levels compared to sham at 24 hours post-injury in all regions except for female PFC and dStr, and male NAc. In the male and female PFC and NAc, compared to sham, there was a significant increase in ROS production between 24 hours and 7 days, followed by a significant decrease from 7 days to 14 days with no difference from sham in the female NAc at 14 days. In the midbrain, ROS significantly decreased from 24 hours to 14 days, with no difference from sham at 14 days in the female group. In male and female dStr, ROS significantly increased from 24 hours to 14 days. These data demonstrate unique patterns of oxidative augmentation across pain and reward regions, which in many cases remained unresolved by 14 days post-injury. Understanding the trajectory of these pathogenic processes can be used to optimize pain interventions post-TBI.

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A43

CURCUMIN PREVENTS THE DEVELOPMENT OF MOTOR DEFICITS IN GFAP-IL 6 MOUSE MODEL WHEN DELIVERED USING MIXED-SURFACE G4 PAMAM DENDRIMERS

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Neuroinflammation is associated with numerous neurodegenerative diseases. Recently established GFAP-IL 6 mouse model congenitally expresses hippocampal and cerebellar neuroinflammation via upregulation of interleukin 6 (IL-6). The IL-6 gene is expressed by astrocytes, leading to low grade chronic activation of astrocytes and microglia due to cytokine induction. Previous studies have identified the potential of curcumin as a promising treatment for neuroinflammation. A natural compound found in turmeric, has gathered attention for its potential anti-neuroinflammatory properties. Notably, curcumin has been shown to effectively reduce astrocyte activation, a key mediator of neuroinflammation. These findings suggest that curcumin may have a beneficial impact on reducing neuroinflammation by modulating astrocytes activity. However, the efficacy of this treatment is hindered by its low bioavailability and solubility. One method to increase the treatment efficacy is to deliver curcumin using a nanoparticle poly-amido(amine) (PAMAM) dendrimers. Generation 4 (G4) 70/30 PAMAM dendrimers contain hydroxyl and amine surface functional groups at a 70:30. In this study, we used G4 70/30-cystamine core PAMAM dendrimer-encapsulated curcumin (D-Curc) for intracranial administration into the hippocampus and cerebellum of the GFAP-IL 6 mouse model. The efficacy of D-Curc was measured by testing motoric and cognitive functioning via accelerated rotarod (accelerod) and water T-maze (WTM) respectively. Prior to treatment administration, a preoperative sex-dependent genotype difference was observed between heterozygous GFAP-IL 6 mice (HET) and wild-type (WT) mice. The female HETs exhibited significantly reduced latency to fall when compared to female WT mice ($p=0.028$); whereas male HETs exhibited significantly greater latency to fall than WT mice ($p=0.021$). After treatment, we observed that control (HETs) injected with Hank's Balanced Salt Solution (HBSS) and the dendrimer alone developed significant motor deficits, whereas HETs injected with D-Curc did not. Finally, no difference was observed between HET and WT WTM performance. To our knowledge, this is the first time that WTM and accelerod tests have been used to characterize the GFAP-IL 6 mouse model of neuroinflammation following treatment with curcumin.

This GFAP-IL6 model was a generous gift from Emeritus Professor Iain L. Campbell, University of Sydney, Australia. Support for this study was provided by the College of Medicine, John G Kulhavi Professorship, Neuroscience Program, E. Malcolm Field and Gary Leo Dunbar endowed Chair in Neuroscience at Central Michigan University.

B30

EFFECT OF ELECTRICAL STIMULATION ON PLEXIFORM NEUROFIBROMA SCHWANN CELLS

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Neurofibromatosis type 1(NF1) is a genetic condition characterized with peripheral nervous system tumors (PNSTs) including plexiform neurofibroma (pNFs).Plexiform Neurofibromas (pNF) are a pathological condition observed at birth in 20-25% NF1 patients.pNFs occur due to increased drive/proliferation of the deranged Schwann Cell (SC) component leading to complications in the perineural environment.pNFs often lead to nerve dysfunction, deformity pain and damage.We are interested in investigating molecular pathways that drive the aberrant proliferation and invasiveness of SCs leading to neurofibromas.Bioengineered conductive polymers have been tested widely for their potential use in nerve regeneration.In this study we characterized the response of SCs isolated from NF1 patients to electrical stimulation through a conductive biopolymer.Hyaluronic acid (HA) nanofibrous scaffolds encapsulated with multiwalled carbon nanotubes (MWCNT) were prepared through electrospinning as previously described.Immortalized NF1 patient derived Schwann cell (NF-SC) line, ipNF95.11b and wild-type SC line (WT), ipn02.8 were characterized in this study. 0.01% HA-CNT fibers were evaluated through attachment, cellular proliferation, response to electrical stimulation and growth factor release experiments.HA, HA-CNT with and without collagen coating were used for attachment experimental.Each well was seeded with 25,000 cells, cultured for 24 hours and fixed and stained. SCs were cultured on collagen-coated HA and HA-CNT fibers for a duration of 72hrs for proliferation. Wells were seeded with 16,000 cells and coverslips were transferred to a fresh plate prior to Alamar blue (AB) assay.All wells were treated with 10% AB for 6h. Metabolic activity of cells was quantified by analyzing the absorbance at 570nm and 600nm.SC lines were cultured on custom stimulation well plates with HA-CNT nanofibers for 24h prior to electrical stimulation (ES). The cells were stimulated at 20Hz biphasic square wave of 200mV/mm and 100mV/mm for 30mins.The stimulated plates and unstimulated controls were incubated for 40h and treated with AB to quantify the cell proliferation post electrical stimulation (ES). Cell supernatants from all wells were collected immediately post stimulation, 24h and 48h post ES.The cell supernatants collected from ES experiments were analyzed through a NGF capture ELISA.The attachment experiment indicated a highly elongated cell morphology on both fiber types in NF-SCs compared to WT-SCs.The proliferation data over a period of 72h time point post-seeding indicates that NF-SCs proliferate faster on HA fibers (16% between 24h and 72h) compared to HA-CNT fibers (4% between 24h and 72h). WT-SCs comparatively had higher proliferation on both fibers, HA (61% between 24h and 72h) and HA-CNT fibers (70% between 24h and 72h).The ES cells showed a less elongated morphology in NF-SCs while stimulated WT-SC had higher cellular spread area and aspect ratio compared to unstimulated cells.NF1 cells proliferate less under stimulated conditions while unstimulated wells had greater proliferation. The ELISA indicated release of NGF on both SC lines post ES at different time points. The NGF levels changed across the 48h time frame post ES on both cell lines. This study characterized the behavior of NF1 patient SCs and highlights the role of ES to reduce the invasive behavior of neurofibroma SCs.

B31

ENGAGING THE ROLE OF PERSONALIZED MEDICINE: IMPACT OF THE RS6265 SNP IN HOST AND DONOR ON DOPAMINE NEURON TRANSPLANATION IN PARKINSON'S DISEASE

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There remains worldwide interest in the therapeutic approach of transplanting new dopamine (DA) neurons to replace those that die in PD. However, like other PD treatments, heterogeneity in clinical responsiveness exists. Previous trials revealed that some graft recipients demonstrated therapeutic benefit, some showed limited to no benefit, and a subpopulation developed a side effect known as graft-induced dyskinesia (GID). To deconstruct this complexity, our lab focuses on the role of the common single nucleotide polymorphism (SNP), rs6265, found in the gene for brain-derived neurotrophic factor (BDNF) which results in decreased BDNF release. Based on the importance of BDNF in DA neuron maturation and function, we hypothesized that decreased BDNF release associated with rs6265 impairs synaptogenesis of grafted DA neurons resulting in suboptimal efficacy and induction of aberrant GID. Using transgenic rs6265 knock-in rats, we recently reported that rats homozygous for the Met risk allele (Met/Met; M/M) engrafted with embryonic DA neurons from wild-type (WT; Val/Val) donors showed paradoxical enhancement of graft function compared to WT hosts engrafted with WT DA neurons. The Met allele was also uniquely associated with GID. To expand understanding of the impact of rs6265 in DA neuron transplantation, the current study examined the impact of rs6265 in both host and donor. WT and M/M rats were rendered unilaterally parkinsonian and evaluated for amelioration of levodopa-induced dyskinesia and amphetamine rotations, our primary and secondary measures of graft function, assessed over 10 weeks post-engraftment. WT and M/M host rats received E14 ventral mesencephalic cells from WT or M/M donors providing six host-donor combinations: WT-Sham (N=7); M/M-Sham (N=8); WT-WT (N=8); M/M-M/M (N=9); M/M-WT (N=8); WT-M/M (N=8). Our findings indicate that functional benefit continues to occur more rapidly in the presence of the Met allele, understanding that this occurs regardless of whether it is present in the host or donor. Curiously, M/M hosts engrafted with WT DA neurons remain the only group that exhibited GID behavior. Given that rs6265 is found within the BDNF pro-domain/pro-peptide, the function of the Met pro-peptide, which is cleaved from the proBDNF molecule, is being investigated. The benefit of the Met allele not only in this grafting paradigm but also its association with enhanced recovery in traumatic brain injury suggests an important role for the Met pro-peptide in neuroregeneration. In regard to GID induction, we hypothesize that diminished levels of mature BDNF (mBDNF) in the rs6265 graft environment prevent graft maturation, resulting in an immature DA neuron phenotype that we have previously reported to be correlated with GID. Studies examining the impact of exogenous mBDNF supplementation on GID status are pending. Collective knowledge gained from these studies could aid in the development of safe, optimized treatments for PD as well as for other neurodegenerative diseases.

B32

DEVELOPING AND IMPROVING A BIOLUMINESCENT GABA SENSOR

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Many neurological diseases such as Alzheimer's Disease, Parkinson's Disease, and autism spectrum disorder have been shown to be caused, in part, by an imbalance of neurotransmitter levels. Expanding on the types of neurotransmitters that can be detected is important to study the causes and treatments of these diseases. In this study, we focus on the amino acid gamma-aminobutyric acid (GABA), which is an inhibitory neurotransmitter found throughout the brain and is involved in many neurological disorders. We developed a variety of genetically encoded bioluminescent GABA sensors that are an attractive alternative to using fluorescent sensors because they do not require an excitation light source, allowing deeper areas of the brain to be recorded without damaging tissue and improving signal-to-noise ratio due to the lack of autofluorescence. We created a library of bioluminescent GABA sensor variants and tested them for improved responses to GABA. Taking bioluminescence readings on a plate reader, we found that the sensors with a mutated GABA binding domain and optimized linkers have higher responses to saturating amounts of GABA than the ones with the native GABA binding protein. To further improve the response of the sensors to GABA with the goal of using them to image brain activity in rodents, we will use rational design to mutate amino acids in different areas of these GABA sensors with the goal of improving response amplitude and signal-to-noise ratio.

B33

ELECTRICAL STIMULATION OF DUAL-LAYER MICROSPHERES FOR CONTROLLED DRUG DELIVERY FOR NERVE REGENERATION

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Peripheral nerve injuries lead to loss of sensation and eventually loss of function. Shorter gaps and defects can be repaired using end-to-end suturing. The gold standard treatment for large sized defects is the use of autologous nerve grafting which can lead to incomplete recovery. Growth factor releasing microspheres (μspheres) can be aligned with nanofibers to enhance neurite growth. The goal of this project is to use electrical stimulation to deliver drugs/growth factors using dual-layered μspheres to promote nerve regeneration and facilitate neurite growth. We have fabricated a dual-layered PLGA-gelatin μsphere with a lower initial drug release controlled by electrical stimulation. The μspheres will be electrospun with hyaluronic acid-carbon nanotube nanofibers that will be electrically stimulated, and release profiles will be evaluated. The drug release will be initiated by hydrolytic degradation of PLGA, and electrical stimulation will activate the gelatin layer to continue and control sustained drug release.
Microsphere fabrication was performed by using 75:25 PLGA via water/oil/water emulsion as previously described by Whitehead et al, 2017. Gelatin layering was added to the μspheres using three methods: (1) Adsorption – dispersing PLGA μspheres into 6% gelatin type A/B bath for 24 hours, (2) Absorption – dispersing freeze dried PLGA μspheres into 6% gelatin type A/B bath for 24 hours, and (3) Chemical Conjugation – dispersing PLGA μspheres into 6% gelatin[A/B]/MES buffer and adding EDC to facilitate conjugation. μspheres were rinsed, centrifuged, and lyophilized. Gelatin concentration was evaluated through BCA assaying and plotted against a standard absorbance to quantify gelatin coating and concentrations.
Gelatin concentration was highest in the absorption method of making the μspheres ($p < 0.05$). Both the adsorption and absorption methods rely on charge interactions between the gelatin and PLGA molecules. Thus, both methods yield larger μspheres with an average diameter of 78 ± 13 μm via adsorption and 89 ± 17 μm via absorption. Carbodiimide conjugation using EDC activates carboxyl groups in PLGA and forms primary amide bonds with gelatin yielding the strongest gelatin to PLGA interactions. This results in smaller μspheres than the other methods at an average 54 ± 9 μm in diameter. Lastly, gelatin type A was shown to have higher concentrations of gelatin per μsphere for each corresponding method. Due to size and stability of the gelatin layer, subsequent testing work will focus on using conjugated microspheres.
This study shows our ability to fabricate dual-layer microspheres that initiated controlled drug release. Gelatin Type A coated PLGA showed the best outcome when comparing gelatin configurations. Our next step will be evaluating drug release from microspheres using an ELISA to determine linearity of the drug release and test electrical stimulation.

B34

ASSESSING A CLINICAL COHORT USING A PLASMA ALZHEIMER'S DISEASE BIOMARKER PANEL

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Background: Biomarker assessments will become an instrumental component of effective clinical management and trial coordination for Alzheimer's Disease (AD) and related dementias and will enable precision medicine approaches to diagnosis and treatment. Plasma offers an inexpensive non-invasive peripheral biofluid for biomarker assessments that can easily be collected longitudinally. The development of ultrasensitive single molecule array (SIMOA) assays has enabled plasma measurements for AD-related blood biomarkers. Indeed, several plasma biomarkers were recently identified as potentially useful for AD and related dementias. However, their utility in additional clinical cohorts requires further investigation.

Methods: Plasma samples were collected from participants clinically diagnosed as cognitively unimpaired (CU; n=170), mild cognitive impairment (MCI; n=104) or probable AD (AD; n=65) from the Michigan ADRC. Levels of total Tau, phospho-tau 181 (pT181), amyloid β40 (Aβ40), amyloid β42 (Aβ42), glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL) were measured using SIMOA. Biomarker levels were compared across diagnostic groups and correlated with cognitive and demographic variables.

Results: Among the biomarkers assessed, results indicated significantly elevated pTau181, GFAP, and NfL in AD compared to CU. These analytes correlated significantly with CDR sum of boxes ($p<0.0001$). There was also a significant reduction in the Aβ42:Aβ40 ratio. Biomarker levels showed no correlation with body mass index (BMI) within diagnostic groups.

Conclusions: Generally, our results align fairly well with other studies using clinical patient cohorts with extensive additional biomarkers (e.g. PET tracer measurements and CSF biomarkers). The AD-associated increase in plasma pT181, GFAP, and NfL levels supports the potential utility of these proteins as useful plasma biomarkers. This biomarker panel did not differentiate between CU and MCI. Additional novel biomarkers may be needed to identify AD and related dementias at early stages of disease.

B35

DEVELOPMENT OF A NOVEL TRANSLATIONAL RAT MODEL OF DEMENTIA WITH LEWY BODIES

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Dementia with Lewy Bodies (DLB) is the second most common neurodegenerative cause of dementia after Alzheimer's disease. Core clinical features of DLB include cognitive dysfunction (variable attention and alertness), rapid eye movement (REM) sleep disorder, recurrent visual hallucinations and spontaneous parkinsonism. Pathologically, DLB is defined by the presence of three proteinopathies: aggregates of beta-amyloid peptides in the form of plaques; hyperphosphorylated tau protein aggregates in the form of neurofibrillary tangles (NFTs); and misfolded and aggregated alpha-synuclein (α-syn) Lewy bodies (LBs). Additionally, most DLB cases display nigrostriatal degeneration. Co-occurrence of LBs, NFTs and plaque pathologies in DLB is particularly prominent in cortical (cingulate, temporo-occipital) and limbic (entorhinal cortex, hippocampus CA1) regions with neuroinflammatory markers frequently observed. Some characteristics of DLB including LB and plaque co-pathologies have been replicated in rodent models. However, no rodent model has recapitulated the full spectrum of DLB namely: 1) progressive LBs, NFTs and plaque co-pathologies in DLB-relevant brain regions; 2) nigrostriatal degeneration; and 3) DLB-relevant behavioral symptomatology. In the present study, we will develop a novel DLB rat model by combining the transgenic (Tg) F344 rat model of Alzheimer's Disease (AD) with specifically staged and targeted intracerebral injections of mouse α-syn preformed fibrils (PFFs). The TgF344-AD rat model expresses mutant human amyloid precursor protein (APPswe) and presenilin 1(PS1ΔE9) genes resulting in age-dependent accumulation of plaques and NFTs, cortical and hippocampal neurodegeneration, and cognitive disturbances. α-syn PFF injections targeted to the nigrostriatal system will result in accumulation of pathological α-syn in cortical, limbic and nigrostriatal regions, followed by nigrostriatal degeneration and motor deficits. Male F344 wildtype (WT) and AD Tg rats will receive bilateral intranigral injections of α-syn PFFs or α-syn monomer (control) at 6 months of age, followed by additional bilateral intrastriatal PFF and monomer injections at 10 months of age. All rats will be assessed for cognitive and motor performance prior to euthanasia at 12 months of age. Based on the pathological and behavioral progression in both models, we hypothesize that PFF injected TgF344-AD rats will exhibit: 1) abundant pathological LBs, NFTs and plaque co-pathologies with upregulation of neuroinflammatory markers in cortical and limbic brain areas; 2) significant degeneration of the nigrostriatal system; and 3) cognitive and motor impairments. Postmortem assessments will focus on the amygdala, entorhinal cortex, cingulate cortex, hippocampus, striatum and substantia nigra to determine the impact of NFTs + plaques, with and without LB co-pathologies; glial reactivity; and neuronal degeneration. A rodent model that integrates the entire repertoire of DLB co-pathologies and related behaviors will increase understanding of the proteinopathy in DLB and facilitate preclinical assessment of novel disease modifying therapies.

B36

WHERE DO PATHOLOGY AND COGNITIVE DECLINE MEET IN ALZHEIMER'S DISEASE?

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Alzheimer’s disease (AD) is characterized clinically by severe cognitive problems and memory impairment and pathologically by two major protein aggregates, amyloid plaques and neurofibrillary tangles (NFTs) formed by aggregation of tau protein. Previous studies have shown that early, soluble forms of pathological tau are more toxic than late-stage tau aggregates. Therefore, we aim to examine the spatiotemporal accrual of early pathological tau moieties in samples of the frontal cortex, posterior cingulate cortex, and precuneus obtained postmortem from cognitively intact control subjects and those who died with early stage or advanced AD. Notably, these three cortical regions comprise a large-scale brain network called “Default mode network (DMN)”. Communication among these DMN hubs is altered very early in AD patients. Hence, our study aims to help understand the relationship between the early pathological tau in the DMN and changes in cognitive functions mediated by these connected brain regions. Using immunohistochemical analysis and custom-made ELISA assays, our findings so far indicate that early pathological tau starts to accumulate in the DMN as early as Braak stage 4 (n=72, p=0.002), which is earlier in the disease process than predicted by Braak NFT staging. Moreover, tau pathology load inversely correlates with antemortem Mini Mental State Exam (MMSE) score, which measures global cognitive status (n=72, p=0.004).

B37

EFHD2 TRANSFORMS MONOMERIC AND FILAMENTOUS TAU INTO TANGLE-LIKE STRUCTURES IN VITRO

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Aggregated tau is the primary pathological culprit in several neurodegenerative disorders, collectively named tauopathies. The best known tauopathy is Alzheimer's Disease (AD). Abnormally modified tau undergoes pathogenic conformational transformations into transmissible toxic oligomers that coalesce into filaments and, ultimately, into intracellular innocuous ultrastructures known as neurofibrillary tangles (NFTs) in AD brain. The evolving premise deems sequestering tau oligomers to filaments and tangles a protective response against cell demise. Nonetheless, the molecular events that regulate the pathological transitions of tau into oligomers and then into NFTs have yet to be unraveled. We discovered EFhd2 as a protein associated with pathological tau in postmortem brains of various tauopathies and a tauopathy mouse model. We demonstrated that EFhd2 transforms the dynamic tau liquid droplets into less dynamic solid-like structures. Herein, we test the hypothesis that EFhd2 induces tau aggregation in vitro in the presence and absence of arachidonic acid (ARA)—a tau filament inducer. Equimolar concentrations of recombinant human EFhd2 (hEFhd2) and full-length tau (hTau40) were incubated for 16 h with and without ARA. Data were collected from three independent experiments. Visualized by electron microscope, hEFhd2 induced the formation of tangle-like structures that are starkly different from ARA-induced tau filaments. Immunogold labeling confirms the colocalization of hEFhd2 and hTau40 in these aggregates. Seeding competency and cellular propagation of EFhd2-induced tangle-like structures were tested using HEK 293 tau biosensor cells that stably express the repeat domain of P301S tau fused with GFP. When the cells are treated with seeding competent tau species (i.e., ARA-induced tau aggregates), GFP-tagged tau monomers sequester into aggregates that appear as bright puncta. In this experiment, cells were treated with 150 nM tau aggregates, or monomers as a negative control, using Lipofectamine2000. After 48 h, cells were fixed, counterstained with DAPI and imaged with a Lionheart FX automated microscope. The quantitative analysis of seeded aggregates (GFP) using Gen5 showed that hEFhd2-hTau40 (with and without ARA) elicited significantly reduced seeded aggregation compared to hTau40-ARA. Our data suggest that EFhd2 promotes the formation of less transmissible tau tangle-like structures. Future in vivo studies will determine the role of EFhd2 on tau-mediated neurodegeneration.

B38

SENSORY PROCESSING AND BEHAVIORS OF CHILDREN: RETROSPECTIVE ANALYSIS OF CLINICAL DATA

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Introduction: One in six children are estimated to have sensory processing challenges. More than two-thirds of children with autism and intellectual/ developmental disabilities are known to also have sensory processing disorders (SPD). While sensory processing is an internal neurological mechanism, it presents externally as behavioral problems. However, we know little about the empirical relationship between SPD and behaviors. Therefore, the purpose of this study is to evaluate the influence of sensory processing profiles on the behaviors of children.

Methods: A cross-sectional retrospective study design was used to evaluate the association of sensory processing profiles with behaviors of children (N =180) attending a pediatric outpatient rehabilitation clinic. The Sensory Processing Measure with 7 domains (social participation, vision, hearing, touch, body awareness, balance, & planning) was used to assess the sensory profiles of children (ages 2-14 years). The Behavioral Assessment System for Children, Version 3 (BASC-3) was used to assess the behavioral profiles of the children across four domains: internalizing and externalizing factors, behavior symptoms index, and adaptive skills.

Results: The most common diagnosis among the children was poor coordination (42.2%) followed by autism (19.4%). The total SPM score and the 7 subscale scores were significantly associated ($p<.001$) with all four BASC-3 domains. The magnitude of the associations of the total SPM score with BASC-3 domains in descending order: behavior symptom index ($r = 0.56$), adaptive skills ($r = -0.54$), externalizing ($r = 0.42$), and internalizing ($r = 0.39$). BASC-3 internalizing subscale had a correlation of 0.5 or higher with only the hearing subscale ($r = 0.52$), while externalizing was associated with social participation ($r = .48$) and body awareness ($r = .55$). The behavior symptom index and adaptive skills subscales had correlations above 0.5 with almost all SPM subscales.

Discussion: The positive associations of the BASC-3 domains (except adaptive skills) with SPM scores indicate that as sensory processing challenges increase, behavioral challenges also increase. The inverse association of SPM scores with adaptive skills indicates that as sensory processing challenges increase, children are likely to have less adaptive skills such as adaptability, social skills, leadership, functional communication, and activities of daily living. Next steps in research will include predictive modeling to examine the predictive validity of SPM and BASC-3.

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B39

IMUNNE MODULATION EFFECTS ON NEUROPLASTICITY IN ZEBRAFISH

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Neuroplasticity is a mechanism by which damage to the nervous system can be repaired and function restored, but full recovery after neuronal damage is elusive for many organisms. Humans have limited neurogenesis in adulthood, unlike zebrafish, who are renowned for persistent neuronal cell turnover and replacement. Chemical lesions damage sensory neurons in the olfactory epithelium and disrupt neuronal organization in the olfactory bulb, but zebrafish recover from this damage in about one week. Although the brain's primary immune cells, phagocytic microglia, are active in pro- and anti-inflammatory functions, their role in zebrafish injury response and neuroplasticity is unclear. Modulating microglial populations with two compounds, to either decrease or increase their activity, illustrates the contribution of these cells to recovery rate. In addition, timing of immune stimulation in relation to damage may also affect rate of recovery. L-clodronate is a drug that specifically targets phagocytic cells for apoptosis, and zymosan is a sterile yeast cell-wall extract that stimulates immune cells into an active state. Immune modulating drugs were delivered starting 24 hours prior to or concurrent with chemical lesioning of the olfactory epithelium. Morphological changes in three olfactory bulb glomeruli from treated and control fish were examined over recovery time to characterize the role of microglia in neuroplasticity.

Detergent was applied to the right olfactory epithelium to damage olfactory sensory neurons, preserving the left side as an internal control. Treated fish received L-clodronate, zymosan, or saline injections at 24 hours prior to lesioning for the pre-treatment groups. Concurrent treatment groups received injections immediately prior to chemical lesioning. Baseline fish were lesioned without immune modulation. Glomerular structures were visualized using antibody-labeled sensory axons in whole brains with confocal microscopy. Glomerular structures were assessed from 4 hours to 7 days post-lesioning for level of damage and were compared to control tissue.

Previous work demonstrated full recovery of lesioned fish in 7 days. A delayed recovery after modulating microglial populations was expected; however, clodronate-treated fish appeared to recover morphology in all three glomerular structures by 4 days, significantly faster than baseline. Additional treatment groups show various recovery time courses. Saline treatment follows a similar response to untreated controls, where damage peaked early and structures were increasingly organized by 7 days. Zymosan treatment showed increased disorganization in both bulbs, although the treated side was more disorganized.

The activity of microglia after neuronal damage can vary dramatically during recovery. As Covid-19 infections have demonstrated, macrophage activation can result in a "cytokine storm" of hyperinflammation or in viral clearance. Zebrafish as a model system can demonstrate how conserved immune system features promote complete recovery in the nervous system of adult mammals, leading to potential treatments for brain injury and disease.

B40

A STRUCTURAL DISSECTION OF SENSORY INNERVATION WITHIN THE MOUSE AIRWAY

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Interoception is a vital process where the brain receives and processes sensory information from inside the body, including sensations like hunger, heart rate, and the urge to breathe. Despite the crucial function breathing plays in sustaining life, surprisingly little is known about how breathing is controlled by the interoceptive signals from the respiratory system. Research in this field is further complicated by the fact that the vagus nerve (cranial nerve X), which carries ascending sensory information from the internal organs, shows significant structural differences between rodent species. Specifically, the nodose and jugular ganglia comprising the vagal ganglia complex have distinct developmental origins and organization that differs between rats, mice, and guinea pigs. In this work, we mapped the neurons associated with spatial respiratory regions in mice to better understand respiratory sensation and establish a foundation for future functional manipulations. We developed surgical methods for targeting neurons in three regions of the respiratory system: the proximal trachea, distal trachea, and distal lung, then used cholera toxin B (CTB) and adeno-associated viruses (AAVs) to fluorescently label the associated neurons. Our tracing experiments revealed that while the majority of fluorescently labeled cell bodies were located within the nodose ganglia, a significant number of labeled neurons were also found in the jugular ganglia. Furthermore, co-localized labeling was observed across the entire vagal ganglia for all conditions in which different fluorescent channels of CTB were injected into two respiratory regions. These results provide insight into potential mechanisms for spatial resolution of stimuli within the airways and establish a crucial foundation to enable future functional manipulations. Additionally, this structural dissection of mouse airway innervation will enable investigations leading to a better understanding of respiratory diseases.

B41

IDENTIFICATION OF AN INHIBITORY CIRCUIT THAT MEDIATES MOTOR INTEGRATION IN THE SOMATOSENSORY CORTEX

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According to the corollary discharge theory, motor centers send signals informing sensory areas of ongoing motor actions, suppressing the expected sensory input. However, the mechanism underlying such suppression within the cortex is unclear. Using optogenetics, we find that input from the whisker primary motor cortex (wM1) activates layer 6(L6) parvalbumin(PV)-expressing inhibitory cells whose axons arborize locally within deep layers more strongly than any other interneuron population in whisker somatosensory cortex. The greater responsiveness of these PV interneurons was not due to unique intrinsic properties or local circuit interactions but was produced by synaptic mechanisms. Notably, vM1 axons made stronger excitatory connections onto these PV cells than other neurons. Recordings in behaving mice also reveal that some excitatory neurons are suppressed before whisking, whereas some PV interneurons increase their activity. Our results provide a synaptic circuit mechanism for motor related corollary discharge in cortex that may help tactile sensation and whisker-dependent behaviors.

B42

ACETYLCHOLINESTERASE REACTIVATION AMELIORATES CHLORPYRIPHOS MEDIATED DOPAMINERGIC CELL LOSS

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Chlorpyrifos (CPF) is an organophosphate pesticide, that is used extensively in many countries. Although banned recently for agricultural use in the U.S.A., exposure is likely to occur through imported food products from other parts of the world. Indiscriminate usage, particularly in crops, has led to CPF exposure in non-target organisms, including humans. CPF's primary mechanism of action entails inhibition of the enzyme acetylcholinesterase. While its primary toxicological impact is observed in acetylcholinergic neurons, emerging evidence also suggests CPF neurotoxicity in dopaminergic neurons. Consequently, we aim to investigate potential interactions between the cholinergic and dopaminergic systems that could influence dopaminergic neurodegeneration. The current study tested the hypothesis of whether alteration in cholinergic transmission can affect CPF-mediated dopaminergic neurotoxicity. We employed pralidoxime chloride (PC), which is an FDA-approved acetylcholinesterase activator used for treatment of organophosphate toxicity. Our results indicate that CPF exerts the least detrimental effect on Cephalic sensilla (CEP) neurons, while significantly impacting posterior deirid (PDE) neurons. These findings were also in agreement with earlier studies conducted in *Caenorhabditis elegans.* It is important to note, and as reported in earlier studies, that the observed effect on PDE neurons may partially be due to developmental delay resulting from CPF exposure. Nevertheless, our most recent experimental results demonstrate that PC administration elicits an ameliorative effect on CPF-mediated neurotoxicity and acetylcholinesterase inhibition is likely to influence dopaminergic neurotoxicity. Notably, CEP neurons show the highest response to the rescuing effects of PC, while PDE exhibits the least susceptibility. Collectively, these findings suggest a modest ameliorative impact of PC on dopaminergic cell loss. Future studies will investigate PC for a similar effect using chlorpyrifos oxon, a more toxic product of CPF metabolism, to further elucidate the underlying mechanisms and expand our understanding pertaining to CPF neurotoxicity.

B43

PERIPHERAL INTERLEUKIN-10 CONTRIBUTES TO SEX DIFFERENCES IN PAIN RESOLUTION

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Pain is closely associated with the immune system, which is well-known to be sexually dimorphic. For these reasons, neuro-immune interactions are suggested to drive sex differences in pain suffering. However, our understanding of the impact of peripheral neuro-immune interactions on sex differences in pain resolution remains limited. Here, we found peripheral interleukin-10 (IL-10) levels are positively correlated to faster pain resolution in humans and less pain in mice. Notably, IL-10 levels were higher in males than females in the pain conditions where males exhibited faster pain resolution. We used an inflammatory pain rodent model and observed that IL-10-producing immune cells in the skin interacted with nociceptors that express IL-10 receptors. Blocking this communication impeded pain resolution. In mice, classical monocytes were the primary source of IL-10-producing immune cells in the skin, and these peripheral monocytes were more prevalent in males than females under pain in both mice and humans. Further, manipulating sex hormone levels in mice affected the level of IL-10, monocytes, and the speed of pain resolution. Our results demonstrate a critical role for peripheral monocytes and IL-10 in the sexual dimorphism of pain resolution, with potential implications for the involvement of sex hormones driving sex differences in pain resolution.

B44

MAST CELLS ARE NECESSARY FOR THE RESOLUTION OF PAIN HYPERSENSITIVITY AFTER SKIN INJURY

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More than 200 million people undergo surgery involving skin incision each year. But clinical pain management after surgery or skin inflammation is far for being successful. Accumulating data have shown that communication between sensory neurons and immune cells plays a critical role in the regulation of chronic pain. However, very few is known about the role of neuro-immune interactions in the skin in postoperative or inflammatory pain models. One immune cell type that resides in the skin and is found located around sensory nerve endings is mast cells. To determine the contribution of mast cells to postoperative and inflammatory pain, we compared wild type (WT) and mast cell deficient (Sash) mice. The resolution of pain hypersensitivity induced by surgical skin incision or injection of complete Freund's adjuvant (CFA) was drastically delayed in Sash mice compared to WT. Additionally, specific ablation of mast cells by diphtheria toxin in Mcpt5Cre-DTR mice delayed the resolution of pain as well. Consistently genetic activation of mast cells fastens the resolution of postoperative pain. To decipher the mechanisms by which mast cells promote the resolution of pain, we performed an immunoassay to screen 60 cytokines in WT and Sash mice following surgical skin incision. We found several cytokines that were upregulated after incision only in WT mice and were absent in Sash mice. We hypothesized that one of these cytokines is required to switch skin infiltrated proinflammatory immune cells to anti-inflammatory phenotype to promote the resolution of pain.

A44

EXTRACTING NEUROIMAGING QUALITY METRICS USING MRIQC

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Introduction: Magnetic resonance imaging (MRI) is a widely used medical imaging technique with neuroimaging applications in both clinical and research settings. However, artifacts that distort the imaging quality (i.e., head motion, poor signal-to-noise (SNR) or contrast-to-noise (CNR)) frequently contribute to poor or unusable data. Typical quality control of MRI data includes post hoc visual inspection, which can be highly subjective and time-consuming and therefore impractical for large datasets. In this proof-of-concept study, we demonstrate an automated way of obtaining objective no-reference image quality metrics (IQMs) for MRI data using the open-source MRI Quality Control tool (MRIQC; Esteban et al., 2017, PLOS One).

Methods: For input data, we used sample BIDS formatted structural MRI (T1-weighted) data from a 25 year-old healthy male from an open-source dataset by Williams et al. (2023, PLOS Biology). First, to ensure proper installation of MRIQC with supporting libraries onto our local server, a containerized version of the software was implemented using Docker. Once installed, with appropriate allocation of memory (12 GB) and defined input and output directories, the program was run using its defined run command specifying memory allocation, respective directories, and the single participant analysis flag. MRIQC was able to successfully apply a machine learning model to derive IQMs from 140 DICOM images (representing slices) in seven minutes.

Results: In the output directory, an HTML file was generated displaying all the DICOM slices side-by-side with extracted IQMs at the bottom detailing a 0.317 coefficient of joint variation (CJV), a 3.81 CNR, and a 14.18 SNR, among other findings. Typically, CJV details head motion, wherein lower values indicate higher quality capture. Conversely, CNR and SNR typically indicate higher quality with higher metric values. Values less than 0.5 were used to indicate high quality CJV, values greater than 2 to indicate high quality CNR, and values greater than 10 to indicate high quality total SNR based on general thresholds extrapolated from the MRIQC documentation.

Discussion: In this proof-of-concept study, we described an open-source library capable of extracting objective image quality metrics from BIDS formatted data using machine learning. This may greatly reduce observer quality assessment time and subjectivity upon assessment. Implications of the functionality of this library include DICOM to quality metric pipelines that involve conversion of participant/patient DICOM files to BIDS formatted data using supplemental libraries heudiconv and dcm2niix with subsequent input into MRIQC. Reading the output file through HTML file scraping with IQM aggregation could display user-friendly summarized metrics within 7 to 10 minutes in an all-in-one platform. This would allow for more effective image capture and potential recapture while the participant/patient is still in the scanner.

A45

ACTIVITY IMAGING AT DEPTH WITH BIOLUMINESCENCE

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Bioluminescence imaging enables data collection with unique advantages relative to other imaging methods. For example, one, two, and three-photon imaging techniques offer single-cell resolution, but the maximum imaging depth is limited to 100, 450, and 1300 µm respectively. Photon scattering and inherent electrical noise limit the capacity of these imaging modalities to capture high signal to noise ratio optical data. Fiber photometry can image at significantly greater depths without cellular resolution. However, it is highly invasive, requiring implantation of an optical fiber. Bioluminescence imaging, on the other hand, provides a high signal-to-noise ratio without light-induced excitation. These characteristics render it suitable for non-invasive imaging of deep neuronal populations. However, imaging relatively fast events (e.g., calcium flux, neurotransmitter release) proves difficult to achieve. This remains a problem due to relatively low photon output at the lower limit of typical hardware detection ranges. To address this limitation, we developed a method to optimize imaging conditions for in vivo bioluminescent activity imaging. We created an assay using an inexpensive, optical brain tissue analogue that is scalable for medium throughput bioluminescence screening. This assay was used to limit-test the detection depth and maximum framerate of bioluminescent light at experimentally relevant tissue depths. Using this protocol, we demonstrated an effective means for increasing the utility of bioluminescent tools.

A46

A NOVEL METHOD FOR MOLECULAR EVOLUTION OF BL-OG COMPONENTS UTILIZING PHOTO-SENSITIVE TRANSCRIPTION FACTOR EL222

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While significant effort has been invested in discovering new optogenetic tools, advances in molecular sciences have enabled us to directly evolve existing bioluminescent-optogenetic (BL-OG) tools to meet our research and therapeutic needs. One such existing protein is the light-sensitive bacterial transcription factor EL222, which is a light-oxygen-voltage (LOV) based protein that homodimerizes in the presence of blue light, enabling transcription of a target sequence. Here, we present improvements in EL222 via a novel method of molecular evolution in mammalian cells. The method, which involves iterative rounds of mutagenesis followed by screening for reporter gene expression in a luminometer, allows us to produce variants with more advantageous activation and deactivation kinetics, altered light sensitivity, and optimized background transcription. As cellular concentrations of particular proteins often play a crucial role in the development of neurodegenerative diseases, such as the role of TFEB in the progression of Alzheimer's disease, our results may have a significant impact on the treatment of neurodegenerative diseases.

B45

IMPROVED BIOLUMINESCENT-OPTOGENETIC TOOLS FOR MANIPULATION OF NEURAL CIRCUITS

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Bioluminescent optogenetic (BL-OG) tools employ biological light generated by luciferase enzymes oxidizing their small molecule substrate, luciferin, to activate light sensing molecules. When combined with ion-moving optogenetic elements, these luciferase-opsin fusions, Luminopsins (LMOs), allow activating and inhibiting neural activity in the brain of behaving animals in a bimodal fashion: Opsins can be activated by light from a physical source or by applying the luciferin, thus expanding optogenetic tools to include a chemogenetic component (Medendorp 2021). Various luciferases have been tethered to opsins, and these LMOs have been applied for excitation and inhibition of targeted neuronal populations in vivo (Berglund 2016, Yu 2019, Park 2020, Berglund 2020, Zenchak 2020, Petersen 2022, Ikefuama 2022). To expand the utility of LMOs we generated a series of combinations of light emitters and light sensors and tested their efficacy for modifying membrane potential in whole-cell patch recordings in HEK cells and in multi electrode arrays (MEAs) in primary neurons. Light emitters were variants of Gaussia, Renilla, and Oplophorus luciferases, either alone or in combination with fluorescent proteins to leverage Förster resonance energy transfer (FRET) for bright light emitters. Light sensors resulting in depolarization or hyperpolarization were native or molecularly evolved channelrhodopsins or pumps, recently described super-sensitive channelrhodopsins, blue- and red-light sensors, and light-sensing G-protein coupled receptors. We also tested different configurations of LMOs, with the luciferase tethered to the opsin via the N-terminus, C-terminus, or both. LMOs were analyzed to gauge effects of bioluminescent response (luciferin application) relative to optogenetic response (LED stimulation). Whole cell voltage patch clamp of HEK cells allowed direct comparison of LED induced photocurrent to the current elicited by substrate application to the same cell. This comparison is quantified through coupling efficiency, the fraction of the maximum photocurrent capable of being produced by biolight. Coupling efficiencies of the initial LMOs 1 (wildtype GLuc-ChR2), 2 (wildtype GLuc-VChR1), and 3 (sbGLuc-VChR1) were 0.1%, 1.2%, and 11%, respectively. Coupling efficiencies of the improved versions are substantially higher (>50%). This set of novel LMOs expands the toolbox for bimodal control of neural activities in the brain.

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B46

DELIVERY OF NOCODAZOLE USING PAMAM DENDRIMER NANOMOLECULES TO IMPROVE SURVIVABILITY OF SCID MICE WITH HUMAN GLIOBLASTOMA

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Glioblastoma (GB) is an aggressive form of brain cancer, which belong the grade IV astrocytoma. Till date, there is no cure for GB. The survival rate of individuals diagnosed with GB is about 12-15 months. Current treatments include use of Temozolamide (TMZ) along with chemotherapy and radiation therapy, and in advanced stages, surgical removal of the tumor is often necessary. In addition, GB has a highly heterogenous population of cells and, currently, the available treatments can target and kill only a sub-population of these cancer cells, while the remaining population of cells continue to proliferate, posing a major risk factor for tumor relapse. Moreover, cancer stem cells (CSCs), which are usually relatively inaccessible tumors, are exceedingly difficult to target and are another major cause for tumor relapse, which is often highly invasive and overly aggressive. Previous pre-clinical and clinical studies have revealed several severe and lasting adverse side effects of TMZ treatment, radiation therapy, and tumor resection. There is a need for more effective treatments for GB, including the use of better delivery systems, to maximize therapeutic efficacy. To this end, we propose Nocodazole, an anti-neoplastic agent that halts proliferation and migration of tumor cells. However, Nocodazole is water insoluble and delivering water insoluble compounds to the brain is a major challenge. Herein, we sought to demonstrate encapsulation of Nocodazole (Noco) within cavities of polyamidoamine (PAMAM) dendrimer nanomolecules (D-Noco) which increases its packaging efficiency, aqueous transport, and eventual release into in vitro U87 human glioblastoma cells lines and in vivo U87 induced tumors in severe combined immunodeficiency disease (NOD.Cg-Prkdcscid/J) mice. Our in vitro results showed that U87 cells treated with D-Noco less survivability compared to the cells treated with free Nocodazole, confirming increased solubility and bioavailability of Nocodazole when encapsulated in the PAMAM dendrimer as compared to its native form. This also confirmed the treatment effects of D-Noco compared to free form Nocodazole in U87 cell lines. As a next step, we injected D-Noco directly into U87 induced brain tumors in NOD.Cg-Prkdcscid/J mice. Following treatment, in vivo imaging was performed to analyze the tumor growth and invasion twice a week until the end of the mice. Kaplan-Meier survival analysis of the mice following tumor formation showed that mice, which received treatment with D-Noco, survived significantly longer than those which did not. Overall, our results suggest that PAMAM dendrimers can improve the solubility and drug-delivering efficacy of water insoluble cancer drugs, such as Nocodazole, both in vitro and in vivo.

B47

MINIMIZING ARTIFACT WITH MULTI-ECHO FMRI DATA ACQUISITION AND PREPROCESSING: AN EXAMPLE IN A STUDY OF CHILDREN AND ADOLESCENTS

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Introduction: Functional magnetic resonance imaging (fMRI) has emerged as an important tool for understanding brain development and the neural bases of psychiatric and neurological disorders. However, head motion and signal dropout are common problems in fMRI research, particularly in pediatric neuroimaging. There is a need for better quality control to reduce noise and improve data quality. Recent advances in data acquisition, particularly multi-echo fMRI, have allowed for data-driven approaches to reduce noise and recover signal in areas of high susceptibility. Here, we describe a novel pipeline for preprocessing, denoising, and quality assurance of multi-echo fMRI data, and examine the effects of this pipeline on head motion and signal dropout in an ongoing pediatric fMRI study.

Methods: Here, we used 166 multi-echo multi-band fMRI scans collected from an ongoing study of participants whose age ranged between 10-17 years old. A custom preprocessing pipeline that implements various AFNI programs along with TE-dependent analysis (tedana) was applied to the acquired fMRI data. Primary outcomes were head motion, measured by framewise displacement (FD) before and after preprocessing. Paired sample t-tests were performed to compare differences in FD from pre- to post-processing. Visual inspection of the data was also used to identify head motion and signal dropout.

Results: Visual inspection shows substantial head motion and signal dropout in areas of high susceptibility (e.g., medial frontal cortex, medial temporal lobe). Following preprocessing, visual inspection shows a blunting of head motion and recovery of signal dropout. Before preprocessing, average head motion ranged from 0.8 to 3.71 mm ($M = 0.33$, $SD = 0.47$). There was a significant reduction in head motion from before to after preprocessing ($M = 0.17$, $SD = 0.17$), $t(165) = 4.56$, $p < 0.001$.

Discussion: Our preprocessing pipeline was associated with a significant reduction in head motion, as well as recovery of signal in areas of high susceptibility. However, the head motion and signal dropout artifacts have not been entirely eliminated from the data, highlighting the need for future improvements. Improving fMRI data quality by minimizing artifact is essential for accurate fMRI data analysis.

A47

THE BRAIN DATA ALCHEMY PROJECT: TEACHING RESEARCH REPRODUCIBILITY AND DISCOVERY SCIENCE WHILE MINING GOLD FROM ARCHIVED GENOMICS DATA

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During the past decade, the landscape of neuroscience research has undergone two major transformations in the way that data are collected, analyzed, and interpreted. First, there has been an intensive push to reform scientific practices to improve research reproducibility. Second, accelerated growth in computing power and omics knowledge has led to a blossoming of “discovery science”. In this new landscape, trainees need to acquire skills that are not included in traditional curriculum. We have addressed this need by creating an intensive summer program that provides direct, hands-on experience with experimental design and statistical issues related to research reproducibility and discovery science. Within the program, trainees conduct a systematic meta-analysis focused on a chosen neuroscience topic using the burgeoning trove (>10,000) of publicly available transcriptional profiling datasets (microarray, RNA-Seq). We successfully piloted the program in 2022 (n=6 trainees). We found that over the course of a single summer (10 weeks), trainees were able to learn to code in R, survey literature, and run a full genomics meta-analysis that could serve as a small publication or preliminary data for a grant. The topics chosen by the trainees included chronic stress, sleep deprivation, antidepressant usage, viral and bacterial inflammation. Next year, we plan to focus on substance use. Each of the meta-analyses revealed an extensive set of differentially expressed genes that can shed light on neuropsychiatric disorders. These gene sets will be released within reference databases compiled by the PI (Brain.gmt) and broader curation efforts (Geneweaver, MSigDB, Enrichr, PhenoCarta) to advance genomic science.