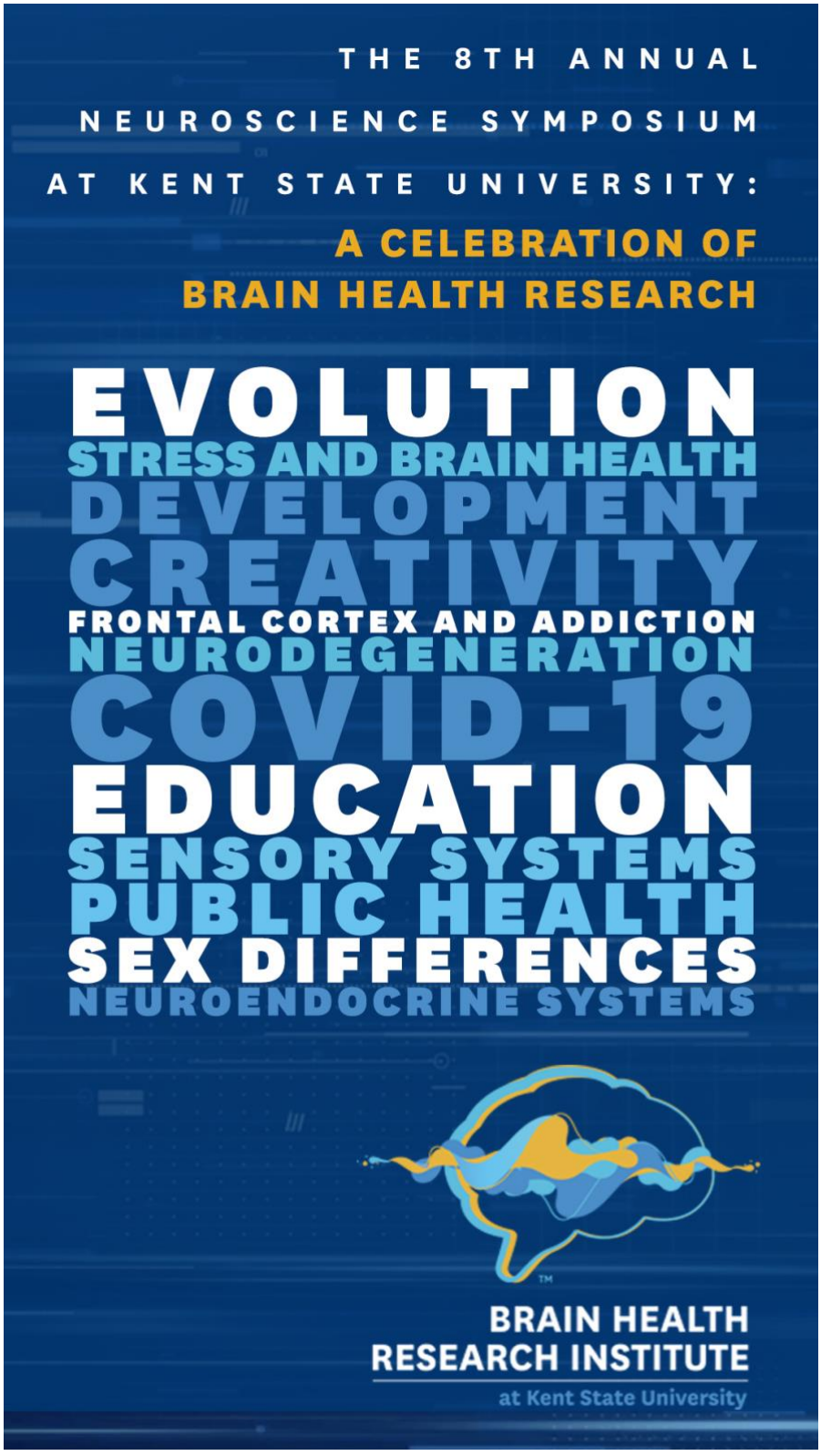
Trainee Abstracts

October 8-9, 2020



Abstracts are ordered alphabetically. A * indicates the trainee author and a 📣 indicates that the abstract is being presented as a talk during the symposium

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Doctoral Student

Dscam overexpression impairs neuronal morphology during development

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Down syndrome (DS) results from the triplication of human chromosome 21 (HSA21). It affects 1 in every 700 live births within the United States and is the most common genetic cause of intellectual disability. Multiple genes are implicated in this phenotype, including Down Syndrome Cell Adhesion Molecule (DSCAM). DSCAM is located on HSA21 and regulates the formation of neuronal connectivity in the developing brain. DSCAM is a member of the immunoglobulin superfamily, a transmembrane protein and can act as a receptor for the axon guidance molecule netrin-1. Here, we focus on the effects of Dscam overexpression, which occurs in DS. Our lab has previously shown that Dscam mRNA is locally translated within growth cones, and dysregulation of this process interferes with proper axon growth. In the current study, we used two different models: 1) Dscam gain-of-function mice, which mimic the DSCAM overexpression occurring in DS, and 2) neurons derived from human induced pluripotent stem cells (hiPSCs), which were created from apparently healthy individuals and individuals with DS. In the experiments using Dscam gain-of-function mice, hippocampal neurons were isolated from E17 mouse pups and cultured for 2 days *in vitro*. We found that overexpression of DSCAM leads to stunted axon growth and alters axon branching in vitro. We also observed a reduction in the soma area. Additionally, there was a significant reduction in the number of dendrites and total neurite length. In the experiments using hiPSC-derived DS neurons, we observed a reduction in axon length and impaired axon branching. These neurons also had a smaller soma area and a reduction in total neurite length. Thus, axon growth, branching, total neurite length and soma area were impaired in both Dscam gain-of-function mice and hiPSC-derived DS neurons. These types of changes in neuronal morphology can lead to altered neuronal connectivity. Taken together, these results suggest that Dscam plays an important role in the development of neuronal networks and could be a potential contributor to the connectivity deficits that occur in DS.

Doctoral Student

Briefly disrupting oxytocin receptor signaling in the embryonic mouse brain disrupts sex-specific behaviors in adulthood

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Oxytocin (Oxt) is a neuromodulator of social behaviors in adults, but there is evidence the Oxt system helps shape the social brain during early development. For example, mice with a lifelong disruption of the Oxt receptor (Oxtr) have behavioral deficits not observed in those whose Oxtr is disrupted postnatally. Moreover, neonatal alterations of the Oxt system result in sex-specific

changes in adult behavior. Together, these studies suggest a role for the Oxt system in the formation of sex-specific neural circuitry important to adult social behavior. Based partly on these prior studies, as well as work from our lab demonstrating sex differences in the embryonic development of the murine Oxt system, we sought to functionally link the embryonic Oxt system with adult social behaviors. We hypothesized that transient disruptions of Oxtr signaling during embryonic development would result in sex-specific disruptions in adult behaviors. To test this hypothesis, we performed transuterine microinjections of saline or an Oxtr antagonist into the lateral ventricles of embryonic day (E) 16.5 C57BL/6J mice and observed their behavior in adulthood. In males, we found that this transient disruption resulted in increased aggression and depressive-like behaviors, the latter of which is linked with social behavior deficits. In females, we observed impaired social memory, but no other changes in behavior compared to males. While additional investigation is needed to determine how the embryonic Oxt system affects adult behavior, our results suggest the embryonic Oxt system guides the sex-specific organization of neural circuits important for the neural regulation of social behaviors.

Doctoral Student

A high salt diet influences stress responding

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Consuming excess salt (NaCl), the primary source of dietary sodium (Na), has become prevalent in modern society. Across species, most research on salt consumption has focused on physiology. As a result, current health guidelines advise reduced sodium intake to attenuate risk for cardiovascular diseases. In contrast, research has seldom examined how salt intake affects brain health, and consequently, behavior. Studying the effects of salt intake will provide essential information about how this prevalent, non-caloric component of diet impacts neurophysiology to shift basic behaviors. Given the challenges of manipulating human salt intake, we are using mice so that salt intake can be rigorously monitored. Adult (10 wk old) male C57BL/6J mice had access to one or two calorically equivalent diets differing in salt content. Control diet was 0.4% (w/w) NaCl, and high salt diet was 4.0% NaCl. For 4 weeks, mice received either: control diet only; high salt diet only; both control and high salt diets (mixed); this last allowed analysis of diet preference over time. Diet consumption was recorded twice a week. On the final day of the diet manipulation, environmental threat response was assessed using a swim stressor. Experiments are ongoing, but preliminary results indicate a significant increase in latency to first immobility for mice in the high salt condition compared to control. In other words, continued consumption of salt might extend responses to environmental stressors. Mice that had access to both diets initially preferred the control diet, but over time consumed equivalent amounts of both diets. Ongoing experiments are looking at a longer time period (8 wks) to see how preference for salt in the diet progresses in the mixed group. We are also examining neuroactivation and neuroinflammation in brain regions associated with homeostatic control, stress responses, and behavioral inhibition. Finally, current experiments are examining the behavioral consequences of consuming a high salt diet in female mice, exploring the neurobehavioral effects of salt in a sex that has rarely been studied for this

purpose. Overall, our early findings indicate that elevated consumption of salt could be having profound influences on basic mammalian behaviors.

Doctoral Student

Wnt/β-catenin canonical pathway changes in brain and bone of an amyloid-dominant mouse model of Alzheimer's disease

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Patients with Alzheimer's disease (AD) are at increased risk for osteoporosis and bone fracture compared to neurotypical patients of the same age. This comorbidity negatively impacts quality of life in these patients and has been linked to increased mortality. As AD is the leading cause of dementia and currently affects almost 6 million Americans, it is essential to identify mechanistic linkages between loss of bone integrity and neurodegeneration in this disease. The central and peripheral nervous systems regulate bone remodeling through complex circuitry and cell signaling pathways. One such pathway, canonical Wnt signaling, is also shown to be disrupted in AD. Therefore, we hypothesized that deficits in Wnt/β-catenin signaling would be associated with both bone loss and amyloid-β neuropathology in a rodent AD model that presents with low bone density, APP/PS1dE9 mice. Using radiographic bone densitometry, we tracked changes in bone density and body composition across increasing pathological stages (2-13 months of age) in these mice. We also collected brain and bone tissue for subsequent assays to measure protein and gene expression associated with the Wnt/β-catenin signaling pathway. Results were assessed for each sex across pathological ages in comparison to sex and age-matched wildtype controls. Our preliminary results confirm evidence of a low bone density phenotype in APP/PS1dE9 mice and ongoing work will address whether disruption in canonical Wnt signaling variables is associated with this low bone mass phenotype.

Doctoral Student

Regulation of peripheral metabolism and Alzheimer's disease pathology mediated by CNS amylin receptors in APP/PS1 mice

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Kent State University

Background: Amylin, a pancreatic hormone, known to regulate glucose homeostasis through its ability to sensitize insulin also acts as a satiety signal in conjunction with leptin. Interestingly, amylin is also an amyloid protein like amyloid-beta (Aβ) and, has been shown to be toxic when aggregated. Furthermore, amylin has also been shown by us and others to be neuroprotective in a non-aggregated state in Alzheimer's disease (AD)-modeled mice. The amylin receptor (AMYR) is expressed throughout the brain, including areas important in both cognition and AD pathology, like the hippocampus. We have previously shown that an analogue of amylin, Pramlintide (PRAM), reduces Aβ plaque burden and recuses hippocampal-dependent cognitive decline in AD-mouse models. However, while beneficial in therapy, how PRAM signaling via AMYR to reduce Aβ burden remains largely unknown.

Method: Here we begin to address whether peripheral regulation of metabolism via the hypothalamus or other mechanisms in regions like the hippocampus are responsible for pramlintide neuroprotection. To address this question, male and female APP/PS1 mice were treated chronically with PRAM or saline peripherally in the presence or absence of AC187, an AMYR antagonist, delivered centrally.
Results: Components of the AMYR are upregulated in the hypothalamus due to chronic PRAM treatment; however, does not appear to have overall effects on glucose or insulin tolerance response. Alternatively, PRAM reduces soluble AB1-42 in the cortex and increases alpha secretase in the hippocampus showing that the two mechanisms of PRAM may be independent of each other.
Conclusion: Our data thus far suggests differential effects of peripheral amylin and even AMYR activation or antagonism on cognitive behavior, APP processing enzymes, and soluble amyloid-beta levels when in the presence or absence of receptor antagonism.

Undergraduate Student

Behind the "Runner's High": A systematic review on the effects of exercise on the endocannabinoid system

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The endocannabinoid (eCB) system plays a key role in maintaining homeostasis and disruptions in eCB signaling have been linked to obesity, anxiety, and depression. Pharmacological interventions that boost or mimic the effects of eCBs have been shown to have anxiolytic and analgesic effects. Emerging data suggest that behavioral interventions, such as physical exercise, may also boost circulating eCB levels. Indeed, the classic "runner's high" - the sense of wellbeing and mood elevation felt after exercise - is thought to be due, in part, to increasing eCB levels. We conducted a PubMed search to identify original research articles published prior to 9/10/2020 that examined the impact of exercise on circulating eCB levels. The search yielded 255 articles, and 29 articles were included in the final review. Nineteen of the 29 studies included humans (n=11 healthy; n=8 patients with pre-existing conditions) and 11 studies included animals (1 study included both humans and animals). Fourteen of the 29 studies examined acute effects (i.e., a single bout) of exercise and 15 examined chronic effects (i.e., exercise program). Seventeen studies examined running or walking and 12 examined another modality (e.g., resistance exercise, cycling, swimming). All 29 studies reported levels of the eCB anandamide (AEA), and 83% of studies (n=24) reported an increase in AEA following exercise. One study reported no change in AEA levels and four studies reported a decrease in AEA after exercise. The four studies that reported an exercise-related decrease in AEA were , $\geq$ 9 week aerobic exercise programs (e.g., treadmill running). In addition, 82% of studies (n=24) examined other eCBs, such as 2-AG; however, the results were inconsistent. The reviewed studies indicate a consistent increase in circulating AEA levels following acute exercise. Given that elevated eCB levels are linked to improved mood, reduced stress, pain, and anxiety, enhanced memory, and neuroprotection, increases in eCB levels may underlie some of the long-term beneficial effects of exercise on ,"brain health". Interestingly, four studies reported a decrease in baseline AEA

levels following longer-term aerobic exercise programs, suggesting a modulation of baseline eCB system functioning that warrants further study.

Post-Baccalaureate Volunteer

Dopamine receptor polymorphism (DRD4 -521C/T) and responsivity to emotional films and social challenge

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Limited research has investigated the impact of the dopamine receptor D4 (DRD4) gene on affective responses to positive and social stimuli. Research shows variability in DRD4 impacts levels of social bonding under the influence of alcohol and reward processing while gambling, suggesting variation in DRD4 impacts emotions concerning social or rewarding stimuli. The goal of the current study is to examine how DRD4 -521C/T polymorphism (rs1800955) predicts emotional responses to film clips and simulated social interaction. In the current study, one sample of undergraduate students, n = 119, were exposed to emotional film clips and a separate sample of undergraduate students, n = 121, completed a within-subject version of the Cyberball task which simulates peer rejection and acceptance. DNA was extracted from saliva samples in both samples, purified, quantified, and finally diluted to a concentration of 5 ng/μl. Repeated measures ANOVA tested for differences in emotional responsivity by task type and segment. Participants with the C/C genotype reported higher levels of positive affect when compared to other genotypes when exposed to all film clips, $F(2, 117) = 2.73$, $p = .069$, or all stages of Cyberball, $F(2, 119) = 3.02$, $p = .052$. In both samples, there was no effect between genotype and negative emotion. These results were controlled for current symptoms of depression. Results suggest a potential buffering effect because levels of positive affect in individuals with the C/C genotype of the DRD4 -521C/T polymorphism are higher when these individuals are exposed to social rejection or acceptance.

Doctoral Student

Optimizing the SMART dynamic bike to improve motor function in people with Parkinson's disease

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Previous research has shown that dynamic high-cadence cycling can improve motor symptoms of Parkinson's disease such as tremor and bradykinesia. The current hypothesis is that an entropic high rotations per minute (rpm) cadence stimulates neuroplasticity which promotes improvements in both the upper and lower body. However, these improvements were not universal with some participants experiencing greater benefits than others. To gain insight into the "typical" participant that is best suited for dynamic cycling, data from a previous study where individuals with PD rode the dynamic cycle with different resistance settings was utilized. PURPOSE: To examine which variables contribute to greater improvement in symptom scores after one dynamic bike session. We hypothesized that participants who had higher BMI,

increased age, more severe symptoms, and higher PD medication dosages were less likely to see improvements in symptoms. METHODS: One within-subjects study was analyzed using correlational and statistical measures. Participants completed three sessions of dynamic biking under three different bike acceleration and velocity settings (11, 19, 99). RESULTS: There was no significant difference in cadence ($p=0.04$, post-hoc $p>0.1$ at all combinations), entropy of cadence ($p>0.3$), average power ($p>0.5$), effort defined as >65% of positive power ($p>0.5$), or change in UPDRS score ($p>0.5$) between the three bike settings. There was a high correlation ($R2=-0.62$, $p=0.01$) between effort and BMI, which remained significant ($R2=-0.85$, $p<0.005$) for participants who completed all three sessions within 10 days but not for those who took longer to complete the sessions ($R2=-0.59$, $p<0.1$). There was also a significant difference in the change of motor function scores between upper and lower body regions ($p<0.03$), high effort mitigated positive changes. CONCLUSION: Participants have key properties which may determine the amount of change in motor symptoms scores they experience following use of our dynamic bike. Upper body and dopamine nonresponsive items are more likely to improve than lower body and dopamine responsive items.

Masters Student

Gender diverse college students had higher psychological distress than cisgender peers during the novel coronavirus (COVID-19) pandemic

Hunt, Cynthia*; Gibson, Gregory; Vander Horst, Anthony; Cleveland, Kimberly; Wawrosch, Craig; Granot, Maya; Kuhn, Tyler; Woolverton, Christopher; Hughes, Joel
Kent State University

Background: The novel coronavirus (COVID-19) pandemic may be the greatest global biopsychosocial stressor in living memory, triggering anticipation of a “mental health pandemic”. Hardly mentioned during the current COVID-19 pandemic is the effect on gender diverse (GD) populations. We compared levels of psychological distress of GD and cisgender college students at a public, R1, four-year university.
Methods: We surveyed all students enrolled at [redacted for blind review] University in three randomly selected cohorts using QualtricsXM. Cohorts were emailed at weekly intervals on March 18, March 25, and April 1 with two reminder emails at weekly intervals. A total of 30,996 undergraduate and graduate students were emailed and 5,547 valid responses were obtained for a response rate of 17.8% (72% female, 85% white). The survey included demographic questions, self-reported risk of contracting COVID-19, and the Kessler Psychological Distress Scale (K6; $\alpha \pm = 0.87$). The K6 is used to screen for psychological distress annually in the National Health Interview Survey. A score of 13 or greater indicates severe distress (range 0 to 24). Participants reported their gender as male (1), female (2), non-binary (3) or other (4). “Other” responses indicating GD status were coded as (3). GD individuals (n = 83) were matched with male (n = 83) and female (n = 83) peers on survey cohort (1, 2, or 3), race (White v. Nonwhite), age, and student status (Undergrad v. Grad).
Results: GD students report higher psychological distress (M= 12.33, SD= 6.04) than males (M= 6.7, SD= 5.76) and females (M= 8.70, SD= 6.57), as well as similar perceived risk ($p = 0.54$). Nearly half (48.2%) of GD individuals were above the cutoff for severe psychological distress.
Conclusions: Findings of our university survey conducted during the novel coronavirus

pandemic indicated that GD students had very high levels of psychological distress. As the pandemic unfolded, GD students' distress was higher than their cisgender peers. Whether elevated distress will prove transient or sustained requires further study. Although the K6 cannot provide diagnoses, GD students may be at increased risk of mental disorders during the pandemic and may need additional support and expanded access to treatment.

Postdoc

Effects of motor timing training on the golf performance in Parkinson's disease

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Background: Motor timing is essential for improving motor skills and it is critical factor to determine the success in a golf swing. However, individuals with Parkinson's disease have deficits in motor timing due to bradykinesia, tremor, and rigidity. Rehabilitative training that employs a metronome beat to set a rhythm (Interactive Metronome) could provide rehabilitative training to improvement in motor timing and variability in golf performance.
Purpose: The purpose of this study is to investigate the effects of 10 sessions of Interactive Metronome training on motor timing and variability in the golf performance of older adults with Parkinson's disease.
Methods: The participants with Parkinson's disease completed 10 sessions, 35-40 minutes per session, three times a week for 4 weeks. The speed and tempo of the golf swing with a seven iron were measured. . Motor timing was analyzed by using Long-Form assessment (LFA) which evaluates timing and accuracy when performing movement tasks of the hands and feet. The speed and tempo data were obtained using a golf simulator. A paired sample t-test was used to compare the pre and post measure outcomes.
Results: After 10 sessions, there was a significant improvement in motor timing between pre-post testing (pre: 158.16¬±75.05, post: 94.66¬±67.76, t=3.102, p=0.027). However, tempo variability (pre: 22.81¬±14.00, post: 11.05¬±7.16, t=1.739, p=0.143) and speed variability (pre: 5.99¬±3.58, post: 4.49¬±1.81, t-.721, p=0.503) were not significantly different.
Conclusion: These findings indicate that Interactive metronome training can promote improvements in motor timing and golf performance in older adults with Parkinson's disease. In addition, motor timing training could be widely utilized along with the exercise to reduce the symptoms of Parkinson's disease.

Doctoral Student

Tempol administration during acquisition of conditioned place preference abolishes expression of fentanyl-seeking behavior

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Kent State University

Introduction: Accounting for 46,802 deaths in 2018, the opioid epidemic has reached exponential proportions with 67% of deaths resulting from use of synthetic opioids such as fentanyl. The primary cause of opioid overdose and death is opioid-induced respiratory

depression (OIRD). Tempol is a potent antioxidant that promotes the metabolism of reactive species and has been shown to prevent OIRD and abolish expression of cocaine-induced conditioned place preference (CPP; Beiser, Tehila et al. 2017).
Objective: To examine the effect of Tempol administration on CPP acquisition of fentanyl seeking behavior.
Methods: Long-Evans Rats (15male/16female) underwent place conditioning in a three-chamber apparatus for eight days and were divided into 4 groups: 1) saline and saline, 2) tempol and saline, 3) saline and fentanyl, or 4) tempol and fentanyl. Groups received assigned injections in the paired chamber, or saline (ip) and saline (sc) prior to confinement in the unpaired chamber. Conditioning trials were 30 minutes to allow for complete onset and experience of opioid/tempol action. Extinction tests started 48 hours after conditioning. Animals were placed in the central chamber and allowed to freely explore the apparatus for 15 minutes.
Results: In males, tempol pre-treatment prevented acquisition of fentanyl-seeking behavior and facilitated a fentanyl-induced conditioned place aversion (CPA) relative to the saline/fentanyl controls, a trend that persisted with subsequent testing over 91 days. Importantly, this effect was not observed in tempol – saline controls indicating that tempol administration alone had no rewarding or aversive effects. Females failed to show a significant CPP under any treatment condition.
Conclusion: Tempol pre-administration facilitated fentanyl-induced CPA in males, indicating a conditional reaction between fentanyl and/or its intracellular signaling pathways and tempol. These findings agree with tempol-induced disruption of cocaine CPP acquisition (Beiser, Tehila et al., 2017) suggesting that tempol may have therapeutic potential to reduce addiction vulnerability across drug classes. Thus, the metabolism of reactive species may represent a key molecular target for the development of novel therapies in the treatment OIRD and drug-addiction.

Doctoral Student

Tempol co-treatment selectively reverses fentanyl induced changes in intrinsic cellular activity and signaling in the prefrontal cortex

Knauss, Zackery T.*; Mueller, Devin; Damron, Derek
Kent State University

Introduction: Accounting for 46,802 deaths in 2018, the opioid epidemic has reached exponential proportions with 67% of deaths resulting from use of synthetic opioids such as fentanyl. The primary cause of opioid-related overdose and death is opioid-induced respiratory depression (OIRD). Opioids are known to alter neuronal excitability states through changes in Ca2+ signaling dynamics impacting; neurotransmitter release, internal signaling cascades and short- and long-term cellular function. Tempol is a potent antioxidant that promotes the metabolism of reactive species and has been shown to prevent OIRD without precipitating withdraw, interfering with opioid-induced analgesia, and attenuates cocaine-associated oxidative damage in the prefrontal cortex PFC (Beiser, Tehila et al. 2017).
Objective: To examine the effect of Tempol co-treatment on fentanyl induced cell-type specific alterations in intrinsic Ca2+ activity from cultured PFC neurons.

Methods: Cortical neurons isolated from rat pups, were cultured on glass coverslips and allowed to form mature synapses over 12 days. On days 13-20 cellular activity was assessed through live-cell fluorescent imaging with calcium sensitive dye (Cal-520AM) under continuous perfusion before (3 minutes), during fentanyl 10nM pre-treatment (11 minutes), during fentanyl and Tempol (100mM) co-treatment (5 minutes), after Tempol washout (9 minutes) and after fentanyl and Tempol washout (8 minutes).
Results: Fentanyl administration resulted a near-to complete inhibition of intrinsic Ca2+ within a subpopulation of cells. Tempol co-treatment normalized intrinsic Ca2+ activity to pre-fentanyl levels in a small subset of fentanyl affected cells which were not reversed by Tempol washout. Interestingly, in the absence of fentanyl Tempol alone showed no change in intrinsic Ca2+ activity from control.
Conclusions: These data provide evidence that Tempol selectively targets a subset of fentanyl-affected cells in the PFC which may contribute to many of the non-analgesic side effects associated with opioid use (i.e. addiction, withdrawal, and OIRD). Thus, the metabolism of reactive species and nitric oxide bioavailability may represent key molecular target(s) for the development of novel therapies in the treatment OIRD and drug-addiction.

Doctoral Student

The effects of sex, age and genotype on neuroinflammation in humanized targeted replacement APOE mice

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Neuroinflammation is implicated in the progression and pathology of several neurodegenerative diseases including Alzheimer's disease (AD). While AD presents differently in individuals, advancing age, female sex and presence of the strongest genetic risk factor, APOE4 (E4) genotype, have been shown to contribute greatly to the increased risk of AD. APOE is predominantly expressed in astrocytes and microglia. These glia from E4 humans and mice have been shown to have a more reactive phenotype compared to APOE3 (E3). We hypothesized that age, sex and APOE genotype modify the response to an inflammatory stimulus, potentially by inducing proinflammatory cytokine production and secretion in a cell-type, sex, and genotype-specific manner. We first sought to define the effects of an inflammatory stimulus on sex-specific E3 and E4 primary microglia (PMG) and astrocytes (PMA). Our findings indicate that both male and female E4 PMG produced at least a 65% greater increase in media nitrite levels than E3 PMG. Additionally, a further increase of 25% was observed in E4 females compared to E4 males. E4 PMA isolated from females produced 140% more media nitrite compared to E3 females. To investigate *in vivo*, male and female humanized targeted replacement E3 and E4 mice at 3 or 16 months of age were injected with LPS (0.5 mg/kg) and sacrificed 4h later. LPS induced a higher expression of Il1b and Tnfa mRNA in the frontal cortex and hippocampus of young and aged E4 mice compared to E3. Il1b expression increased in the hippocampus by ~30-fold and ~40-fold in aged E4 males and females, respectively. In contrast, Il1b was only increased ~15-fold in aged E3 males and females. Similar effects were observed in Tnfa and Il6 expression in the hippocampus ($p<0.001$). In the young cohort, no sex differences were observed, but Il1b and Il6 gene expression in E4 males and

females increased by 2-fold compared to E3. These data indicate that a peripheral LPS challenge induces a higher increase in proinflammatory cytokine mRNA expression in older E4 mice and this effect appears to be sex and region-specific. Together, these data demonstrate that multiple factors contribute to susceptibility to neuroinflammation and provide insight into the role of age, sex and genotype in this susceptibility.

Doctoral Student

The new frontier of neurological disease: mapping topological ADAR editing landscapes with machine learning scaling and modeling to predict biomarkers for depression and suicidal risk

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Psychiatric disorders continue to be a social and economic burden in the United States with suicide as 10th leading cause of death. Furthermore, the atmosphere of social isolation and economic hardship induced by the SARS-CoV-2 pandemic has only further increased rates of depression and suicide. Despite the urgent need for better mental healthcare, little is known about the etiology of depression or suicidal behavior. However, immune activation and chronic low-grade inflammation are thought to play a role in many psychiatric disorders. During innate immune activation, adenosine deaminase acting on RNA (ADAR) expression is upregulated. ADAR deaminates an adenosine to an inosine which then is recognized as a guanine by translational machinery and is an important part of immune response to viral infections. Additionally, ADAR editing is one mechanism of increasing transcriptome diversity especially in the nervous system where some proteins depend on regulated editing for proper function including glutamate and serotonin receptors. With increased ADAR expression there is a potential for altered ADAR editing patterns. These alterations can affect spatio-temporally regulated structure and function of proteins that are crucial for synaptic plasticity. Using publicly available RNA seq datasets originally taken from post-mortem brain samples including both males and females in six different brain regions. We used these datasets to map ADAR editing landscapes creating profiles for individuals with MDD, suicide and age matched controls. We then utilized a unique statistical approach to compare and quantify the profiles with Guttman scaling and random forest modeling. Using this approach, we highlighted 26 editing sites as potential biomarkers found in genes responsible for protein localization, apoptosis, angiogenesis, permeability of the blood brain barrier and synaptic plasticity. The total number of ADAR editing sites in the transcriptome and Guttman scaling scores from the excitome can also be used as biomarker to predict suicidal risk. These biomarkers not only give insight into the molecular mechanisms underpinning depression and suicidal behavior but can also provide guidance in a clinical setting for diagnosis, prognosis and therapy for MDD or suicidal risk.

Undergraduate Student

Mitochondrial dysfunction in Alzheimer's disease

McDonough, Jennifer; Richardson, Courtnai*; Sternbach, Sarah

Kent State University

The goal of my research is to identify therapies for Alzheimer's disease (AD). Many studies have shown that mitochondrial dysfunction represents an early pathological change in this disease. Mitochondrial dysfunction causes a decrease in the energy supply which causes damage and loss of neurons. Previous research in our lab has shown that dysregulation of one-carbon metabolism is linked to mitochondrial deficits in neurodegenerative disease. This causes a loss of histone methylation and changes in gene expression that lead to the accumulation of damaged mitochondria in the cell. These damaged mitochondria in AD are smaller than normal mitochondria as a result of increased fission by the fission protein DRP1. These smaller mitochondria are unable to generate sufficient energy. We have found that boosting one-carbon metabolism with the methyl donor betaine increases mitochondrial energy production in the APP/PS1 mouse model of AD. We are now investigating the mechanisms of this effect of betaine in brain regions relevant to learning and memory (cortex, hippocampus) in APP/PS1 mice. In the current studies, control mice and APP/PS1 mice were given regular water or betaine (1%) in drinking water for 1 month or 3 months (n=3). Mice were then sacrificed and cortices were removed. Protein was isolated and separated into cytoplasmic, nuclear, and mitochondrial fractions. The effects of betaine on the interaction of the mitochondrial fission protein Drp1 with mitochondria were then tested by Western blotting. Overall, I found that there is a trend toward reduced Drp1 interacting with mitochondria in betaine treated mice suggesting that betaine is restoring mitochondrial dynamics. Future studies will examine the effects of betaine on mitochondria in the hippocampus and on mitochondrial size by transmission electron microscopy.

Doctoral Student

CD36-mediated retinal ganglion cell loss and gliosis following exposure to exogenous amyloid-beta

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The pathological peptide amyloid beta (Aβ) accumulates in the retina early in Alzheimer's disease and glaucoma, yet its contribution to retinal ganglion cell (RGC) degeneration is still unknown. To investigate the impact of Aβ ≤ on the retinofugal projection, we unilaterally injected fibrillized Aβ ≤1-42 into the eye of adult C57BL/6J mice and analyzed the retina, optic nerve (ON), and primary synaptic target, the superior colliculus (SC). Analysis of inflammatory and degenerative markers using multichannel immunofluorescence indicated that retinal exposure to Aβ ≤ induced microglial activation and RGC death as early as 1 week post-injection. Multiplex protein quantitation of Aβ ≤1-42 peptides demonstrated an increase in Aβ ≤1-42 in the ON and SC of injected retinas, and immunofluorescence confirmed co-localization of Aβ ≤ with microglia in these structures. Intriguingly, unilateral Aβ ≤ eye injections also stimulated an inflammatory response and RGC death in the opposite, un-injected retinal projection. Due to the strong microglial response and co-localization with Aβ ≤, we repeated these methods in mice lacking the Aβ ≤-binding microglial scavenger receptor, cluster of differentiation 36 (CD36). CD36 null mice did not show the RGC loss and microgliosis previously seen in C57BL/6J

mice. These results suggest that retinal Aβ ≤ exposure induces RGC degeneration, and CD36 may serve as a promising target to prevent or slow the progression of Aβ ≤-mediated RGC death and vision loss.

Doctoral Student

Oxytocin receptors in both males and females are functional during embryonic development

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Previous studies suggest that during embryonic development the brain hormone oxytocin (Oxt) contributes to the organization of sex-specific neural circuitry. Some of these effects are thought to be mediated by Oxt's actions on its only identified receptor, the Oxtr. The Oxtr is present as early as embryonic day (E)16.5, while the production of Oxt itself is offset temporally and in sex specific ways; i.e. mRNA for Oxt can be found at E12.5 in females and postnatal day 2 in males. However, it is unknown as to whether or not the Oxtr is functional at E16.5 and capable of transducing a signal. Thus, in order to assess the functionality of the Oxtr at E16.5 we performed an Oxtr-stimulated g-protein coupled receptor binding assay. Our data suggest that the Oxtr is functional in both males and females at this embryonic timepoint. Looking forward we will be investigating the how Oxtr signaling during embryonic development contributes to the organization of sex-specific neural circuits, which ultimately impact displays of behavior later in life.

Undergraduate Student

Oxytocin receptor knockout males seek fewer interactions in a neutral arena aggression test

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Oxytocin (Oxt) is known for its neuromodulatory effects on social behaviors. These effects are mediated by the Oxt receptor (Oxtr), and when its signal is disrupted so too is the expression of social behaviors. For example, transgenic mice with lifelong genetic deletion of the Oxtr, i.e. Oxtr -/- mice, are frequently reported to display increased aggressive behaviors. Work from our lab and others has shown that during resident-intruder tests, Oxtr -/- mice have heightened inter-male aggression. However, in this type of test the experimental animal has an advantage as the test takes place in the subject's home cage. An assessment of the extent to which the Oxt system impacts inter-male aggression has yet to be explored in a neutral arena, where this aforementioned advantage is not present. Based on previous work demonstrating an increase in aggression among Oxtr -/- males, we sought to examine how a deficit in Oxtr signaling alters inter-male aggression during a neutral arena aggression test. We hypothesized that male Oxtr -/- mice would exhibit heightened aggressive behavior compared to Oxtr wildtype (+/+) mice even in a neutral arena. To test this, either adult male Oxtr +/+ or Oxtr -/- mice were placed

along with an adult male stimulus animal into a clean cage simultaneously and their behavior recorded so their interactions could be scored later. This test was repeated once a day for three days. We found that on day one, Oxtr -/- mice spend a significantly greater time being nonsocial than Oxtr +/+ mice, and that Oxtr +/+ mice spend significantly more time in anogenital contact than Oxtr -/- mice did with the stimulus males. On days two and three, none of the measured behaviors were significantly different between genotypes. These results indicate that disrupted Oxtr signaling impacts inter-male aggression in a context-specific manner and may play a greater role in territorial aggression than other types of inter-male interactions. More work must be done to tease apart the ways in which the Oxt system influences male-typical behaviors.