2nd Annual Alcohol & Addiction Research Symposium

November 16, 2018
BioScience Research Collaborative

Gulf Coast Consortia
Quantitative Biomedical Sciences
Conference Sponsor:
The Gulf Coast Consortia (GCC), is a dynamic, multi-institution collaboration of basic and translational scientists, researchers, clinicians and students in the quantitative biomedical sciences, who benefit from joint training programs, topic-focused research consortia, shared facilities and equipment, and exchange of scientific knowledge.

**GCC Research Consortia** include Regenerative Medicine, Translational Pain Research, Mental Health Research, Theoretical and Computational Neuroscience, NanoX, Alcohol and Addiction Research, Chemical Genomics, and Antimicrobial Resistance.

**GCC Training Programs** currently focus on Biomedical Informatics, Computational Cancer Biology, Molecular Biophysics, Neuroengineering, Pharmacological Sciences, and Precision Environmental Health Sciences.

Current members of the GCC Research Consortia include Baylor College of Medicine, Rice University, University of Houston, The University of Texas Health Science Center at Houston, The University of Texas Medical Branch at Galveston, The University of Texas M. D. Anderson Cancer Center, The Institute of Biosciences and Technology of Texas A&M Health Science Center.
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<td><em>Serotonin Receptor Dynamics and Neurocircuitry in Relapse Vulnerability</em></td>
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<td><em>Presynaptic Munc13-1 Binds Ethanol and Affects Ethanol Sedation Sensitivity</em></td>
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<td><em>Cocaine Cue Reactivity and Impulsivity are Linked Processes Underlying Relapse-Related Behavior</em></td>
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<td><em>Methamphetamine Exposure and Withdrawal Impact Gut Microbiota and Induce Depressive-like Behavioral Effects in Rodents</em></td>
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<td><em>A Power Analysis for the Late Positive Potential (LPP): Optimizing Human Cue Reactivity Paradigms</em></td>
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Candidate Gene Targets Identified in the Rat Medial Prefrontal Cortex (mPFC) Associated with Impulsivity
Christina Merritt, UT Medical Branch at Galveston

2:00 Clinical Studies
Convener: Scott Lane, UTHealth

Using a Neuroaffective Biomarker to Match Smokers to Treatment: Results from a New Clinical Trial
Francesco Versace, MD Anderson

2:20 Opioid Misuse Risk in Trauma Patients
Angela Heads, UTHealth

2:40 Technology and Innovation
Convener: Richard De La Garza, Baylor College of Medicine

Inside the TMC Innovation Institute: Houston’s Home to Healthcare Startups
Gwynneth Ballentine, TMCX

3:00 Anti-Addiction Vaccines: Bringing them to Market
Thomas Kosten, Baylor College of Medicine

3:20 Phytocannabinoids and the Global Paradigm Shift
Jokūbas Žiburkus, University of Houston

3:40 Networking and Coffee Break

4:00 Keck Seminar Keynote: Can Tech Treat Alcoholism – The Ria Technologically Enabled AUD Treatment Solution
John Mendelson, Ria Health

5:00 Reception
Roger Little has over 20 years of experience in the neuroscience, and genetics of psychiatric and neurological disorders; 15 years of which have been at the NIH. He is currently the Deputy Director of the Division of Neuroscience and Behavior (https://www.drugabuse.gov/about-nida/organization/divisions/division-basic-neuroscience-behavioral-research-dbnbr/office-director-od). He oversees a $375 million extramural research portfolio in basic neuroscience research in addiction, pain, and HIV-AIDs. Previously he was a Senior Advisor at the National Institute of Mental Health and served as a liaison and coordinator for trans-NIH initiatives and had a leadership role for the Common Fund Genes, Tissue, and Expression initiative (https://commonfund.nih.gov/GTEx/index). He led a group that developed a new model for brain banking at NIH which is called the NIH Neurobiobank (https://neurobiobank.nih.gov) which is a network of 6 federated brain banks that provide access to post-mortem human brain for researchers, and information to the disease advocacy community and the public. In its first 4 years of operation it has accepted over 2400 human donors and over 30 different addiction, neurological, and psychiatric disorders. Dr. Little has been recognized with over 30 awards since he began at the NIH and serves on the Science Advisory Committee of the National Disease Research Interchange.

Roger received his B.S. in Biology and English from the University of Vermont and his M.S. in Neurotoxicology and Ph.D. in Molecular Neurobiology from New York University. His doctoral work involved cloning and characterizing a novel G-coupled protein receptor which was identified because it is a receptor for one of the toxins in black widow spider venom. His Masters work involved the signaling mechanisms involved in astroglial activation following brain injury.

Abstract:
Dr. Little’s talk will cover developments NIDA funding priorities as informed by changes in state marijuana policies, the opioid crisis, and opportunities based on new scientific developments and breakthroughs; spanning the NIDA portfolio of basic neuroscience, prevention, and treatment of substance use disorders. He will discuss future directions for research as it relates to substance use disorders, HIV-AIDs, and pain research at the NIDA.
Abstract:
The gut microbiota has recently gained attention as a possible modulator of brain activity. A number of reports suggest that the microbiota may be associated with neuropsychiatric conditions such as major depressive disorder, autism, and anxiety. Among other possible mechanisms, the gut microbiota is thought to influence the brain via vagus nerve signaling. The insula, which is important in addiction and specifically in tobacco withdrawal symptoms, processes and integrates these vagal signals. To determine if microbiota diversity and structure modulate brain activity, we collected fecal samples and examined insular function using resting state functional connectivity (RSFC). Thirty healthy participants (non-smokers, tobacco smokers, and electronic cigarette users, n=10 each) were studied. We found that the RSFC between the insula and several regions (frontal pole left, lateral occipital cortex right, lingual gyrus right, and cerebellum 4, 5 and vermis 9) were associated with bacterial microbiota diversity and structure. In addition, two specific bacteria genera, Prevotella and Bacteroides, had different abundance in tobacco smokers as compared with non-smokers and electronic cigarette users. Abundance of Prevotella and Bacteroides also associated with insular resting connectivity. In conclusion, we show that insular connectivity is associated with microbiota diversity, structure, and at least two specific bacteria genera. Furthermore, this association is potentially modulated by tobacco smoking. While replication is necessary, the microbiota is a readily accessible therapeutic target for modulating insular connectivity, which has previously been shown to be abnormal in anxiety and tobacco use disorders.
Dr. Anastasio’s research interests lie at the interface of pharmacology, neuroscience, and psychiatry and have evolved to a primary focus on elucidating the molecular, neurochemical and behavioral underpinnings of impulsivity, a trait that has been implicated as an important risk factor and contributor to relapse for addictions, obesity and eating disorders. She joined the Faculty of the UTMB Department of Pharmacology and Toxicology in 2014 and has full membership in the UTMB Center for Addiction Research. Her studies take a multi-disciplinary approach (e.g., biochemistry, epigenetics, cellular models, gene-mediated viral delivery, behavioral models) to elucidate the neurobiological substrates within the corticostrital circuit that drive the vulnerable vs. resistant phenotypes underlying dysregulated drug- and feeding-related behaviors as assessed in the preclinical environment.

Abstract:
The drug overdose crisis and limited access to therapeutics for substance use disorders (SUDs) has crystallized a focus on enhancing the mechanistic understanding of SUD neurobiology to identify new diagnostic and therapeutic approaches. A diagnostic hallmark of SUDs is impulsivity, manifested as “continued drug use despite adverse consequences”. Core deficits in ability to inhibit behavior and misdirected attention underlie the correlation between motor impulsivity and elevated cue reactivity (attentional bias toward drug reward stimuli). The ‘expanding cycle of dysfunction’ associated with SUDs is linked to neuroplasticity within the prefrontal cortex (PFC) and its directional and bidirectional connectivity to other cortical regions, the basal ganglia, amygdala and hippocampal formation. Serotonin (5-HT) is an important, but underappreciated, neuromodulator and its involvement in SUDs is gaining appreciation, however, its complexity of actions continues to challenge a clear understanding of the multiplicity of its role in SUD neurobiology. Preclinical studies implicate 5-HT as an influential regulator of neural circuit dynamics involved in the SUD cycle. New discoveries pioneered by our team implicate a strategic role for the G protein-coupled receptors (GPCRs) 5-HT2A receptor (5-HT2AR) and 5-HT2CR to control neural mechanisms underlying relapse vulnerability to cocaine and opioids. These GPCRs act via the “receptorosome,” the composition of membrane, cytosolic and accessory proteins through which protein-protein interactions (PPIs) interface GPCR coupling to downstream signaling cascades. We propose the engagement of these GPCRs, associated signaling processes, and their interactions, is a rich opportunity to understand these systems in humans, rodents and cells, and to further mine this understanding for new targets to modify key neurobiological features of SUDs across classes of abused drugs.
Dr. Joydip Das is currently a professor at the Department of Pharmacological and Pharmaceutical Sciences, University of Houston. He received his Ph.D. from Indian Institute of Technology, Bombay, and later trained at the Massachusetts Institute of Technology and Massachusetts General Hospital. His current research goal is to identify presynaptic targets of alcohol in the brain with a long term goal of developing drugs for alcohol use disorder. Dr. Das is the Editor-in-Chief of the Journal of Addiction and Dependence. He serves as an ad-hoc reviewer of NIH study section and his research is funded by NIH.

Abstract:
Munc13-1 is a presynaptic protein which plays an essential role in synaptic vesicle priming. Using diazirine-based azalcohols we identified Glu-582 as the alcohol-binding residue in the C1 domain of Munc13-1. Ethanol binding to the Munc13-1 C1 domain reduces diacylglycerol binding, which is predicted to reduce the activity of Munc13-1 and presynaptic release. Using Drosophila as a model system, we show that the Dunc-13^{P84200/+} heterozygotes display a very robust increase in ethanol self-administration. Sedating concentrations of ethanol significantly reduce synaptic vesicle release in olfactory sensory neurons. Drosophila haploinsufficient for the Munc13-1 ortholog Dunc13, are more resistant to the effect of ethanol on presynaptic inhibition. Genetically reducing the activity of Dunc13 through mutation or expression of RNAi transgenes also leads to a significant resistance to the sedative effects of ethanol. We propose that reducing Dunc13 activity, genetically or pharmacologically by ethanol binding to the C1 domain of Munc13-1/Dunc13, promotes a homeostatic response that leads to ethanol tolerance.
Kelly Dineley, Professor
Mitchell Center for Neurodegenerative Disorders
Center for Addiction Research

*PPARγ Agonism for Cocaine use Disorder: Mechanistic Insight using Preclinical Models*

Dr. Kelly Dineley attended the University of the Pacific in Stockton, California, where she received her BA in 1983 (Biology) and her MS in 1986 (Cell Biology). In 1998, she received her PhD in Neuroscience from Baylor College of Medicine in Houston, Texas. Following a postdoctoral fellowship in neurobehavior, Dr. Dineley joined the faculty ranks at the University of Texas Medical Branch (UTMB) in 2003. She has steadily funded her research with grants from the National Institutes of Health, the John Sealy Memorial Endowment Fund for Biomedical Research, the Dunn Foundation, the Brown Foundation, Inc., the Alzheimer’s Association, the Bright Focus Foundation, the Peter F. McManus Foundation, and the Mohn Foundation.

Abstract:
Background. Chronic cocaine use causes behavioral changes by altering brain structure and function. The rodent self-administration model parallels certain drug seeking behaviors of cocaine-dependent subjects. One notable behavior is increased responsiveness to cocaine-paired cues in the cue reactivity task, a surrogate for self-reported cocaine craving in humans. This responsiveness is particularly observable following forced abstinence. Cocaine self-administering rats treated with a peroxisome proliferator-activated receptor-γ (PPARγ) agonist (pioglitazone) during forced abstinence exhibit significantly attenuated cocaine cue reactivity.

The mechanisms underlying pioglitazone-mediated attenuation of cocaine cue reactivity have yet to be elucidated. Since PPARγ is a transcription factor, one hypothesis is that the mechanism may involve induction of transcriptional targets. Previous work has demonstrated that many of the downstream targets of PPARγ are important to brain structural integrity. Several human studies have demonstrated widespread loss of white and gray matter in individuals with cocaine use disorder. We recently-published a study showing that pioglitazone decreased self-reported craving in subjects with cocaine use disorder simultaneous with improved white matter integrity (e.g., splenium and genu of the corpus callosum, posterior and anterior thalamic radiations). Using the rat self-administration model, we attempted to reveal the underlying structural changes that drive pioglitazone-mediated attenuation of cocaine cue reactivity.

Since PPARγ is involved in a complex with phosphorylated extracellular signal-regulated kinase (phospho-ERK), we explored the putative role of this complex in the mechanism. Phospho-ERK can act upon a signaling cascade which ultimately modulates transcription through cyclic-AMP response elements. Thus, we explored our transcriptomic results for enrichment of putative PPARγ and cyclic-AMP response elements (PPAREs and CREs) in addition to wholistic analyses of the genes regulated by PPARγ agonism. We hypothesized that PPARγ- and ERK-mediated gene transcription attenuates cocaine cue reactivity through remodeling of the structural and functional landscape induced by chronic cocaine use.
Methods. All rodent experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (National Research Council) and with the approval of the Institutional Animal Care and Use Committee at UTMB. Brain tissue from rats that underwent a two-week self-administration paradigm followed by 30 days of forced abstinence and subsequent cue reactivity testing. Upon completion of the behavioral experiments, brains were harvested and used for next generation sequencing, immunohistochemistry, histological staining and immunoblot.

Results. RNA sequencing (RNA-seq) results were robust, identifying 12,036 genes in the hippocampus and 12,014 genes in the medial prefrontal cortex. Of these, 259 of the genes were significantly increased or decreased by PPARγ agonism in the hippocampus and in the prefrontal cortex this number equaled 125. Roughly one-fifth of the genes identified in these brain regions contained PPAR-response elements (PPAREs), evidence that pioglitazone induced PPARγ-dependent gene transcription. Approximately 10% of the genes induced by pioglitazone contained CREs. However, this does not demonstrate enrichment for PPAREs compared to the total population of genes identified.

Further analysis using Ingenuity® Pathway Analysis revealed that genes regulated by PPARγ agonism were particularly involved in cell survival. In contrast to the overall gene population identified with RNA-seq, there was a statistically significant enrichment within cell survival pathways for genes containing PPAREs, suggesting that our hypothesized transcriptional mechanism specifically drives cell survival pathways in distinct brain regions.

Alongside our transcriptomic study, we tested for structural integrity using the Luxol Fast Blue stain and other markers of structural integrity with immunohistochemistry. The Luxol Fast Blue stain results suggest that there is an interactive effect with cocaine and PPARγ agonism in the corpus callosum and in the dentate gyrus of the hippocampus.

Finally, immunoblotting experiments additionally support the hypothesis that structural and functional integrity are improved with PPARγ agonism by identifying alterations of aquaporin 4 and proteolipid protein 1 expression between cocaine self-administering rats treated with pioglitazone or untreated.

Conclusion. Our results support the hypothesis that pioglitazone induces both PPARγ- and ERK-mediated gene transcription to attenuate cocaine cue reactivity through remodeling of the structural and functional landscape induced by chronic cocaine use.
Currently Ms. Campbell is a second-year graduate student in the Pharmacology and Toxicology program at the University of Texas Medical Branch under the mentorship of Dr. Noelle Anastasio. Her current research includes studying the different aspects of cocaine and oxycodone taking and seeking behaviors in high and low impulsive rats.

Abstract:
The trajectory from drug use to addiction begins against a background of vulnerability based upon genetic and environmental factors and progresses as neuronal plasticity (the strengthening or weakening of neuronal activity) in key brain circuits. The cycling progressive nature of substance use disorders (SUDs) stymies efforts to stay abstinent with vulnerability to abuse and relapse during abstinence often precipitated by impulsive behavior. Motor impulsivity (behavioral disinhibition) and impulsive choice (decision-making) are two dimensions of impulsivity that have been associated with addictive behaviors in humans and laboratory animals. Impulsivity is linked to SUDs including cocaine use disorder (CUD). Cocaine-dependent subjects often present with high levels of impulsivity, which is negatively correlated with treatment retention in cocaine-dependent individuals. Impulsive action has been shown to positively correlate with cue reactivity in cocaine-dependent subjects. Preclinical models have shown that impulsivity and cue reactivity are interlocked phenotypes but the exact nature of the relationship between impulsivity and cocaine use is not well understood. It has not been determined whether impulsivity is a factor leading to and/or resulting from withdrawal from cocaine use. Therefore, the objective of the current study was to establish whether impulsivity is a factor that predisposes vulnerability or arises as a result of withdrawal from cocaine. We examined the effects of extended abstinence from cocaine self-administration (SA) on expression of impulsivity by employing the 1-choice serial reaction time (1-CSRT) task to identify motor impulsivity in individual outbred male Sprague-Dawley rats. Following stable responding, the rats are challenged in a session in which the intertrial interval (ITI) is raised from 5 to 8 sec to more easily detect trait impulsivity. The upper and lower 25% of rats were identified as high (HI) or low impulsivity (LI) rats, respectively, based on the number of premature responses. The phenotype is stable in that premature responses in HI rats remained significantly higher vs. LI rats across 75 days of training (p<0.05). Following identification of the HI/LI phenotype and cocaine SA (0.75 mg/kg/inf cocaine; 180 min/day; FR1-5), rats were subject to a forced abstinence (FA) period of 30 days during which daily 1-CSRT task maintenance sessions took place to track the effects of withdrawal from cocaine on impulsivity and additional measures of executive function.
function (e.g., attention, motivation). On FA days 10, 20, and 30, HI and LI rats were subjected to an ITI challenge session (ITI8) in the 1-CSRT task; on FA day 30, a cue reactivity test session immediately followed the ITI challenge session. As predicted, HI rats (identified prior to cocaine self-administration) in FA made more premature responses than LI rats during daily 1-CSRT task maintenance sessions. Interestingly, inherent impulsivity was not altered by the dynamic state of abstinence from cocaine self-administration; the number of premature responses on an ITI8 challenge session (FA day 10 or FA day 20) made by either HI or LI rats in FA was identical to premature responses on an ITI8 challenge session prior to cocaine self-administration. High impulsivity predicted high cocaine-seeking behavior on FA day 30. Thus, high impulsivity appears to be a critical vulnerability factor leading to higher relapse-like behaviors.

Shadab Forouzan, University of Houston

*Methamphetamine Exposure and Withdrawal Impact Gut Microbiota and Induce Depressive-like Behavioral Effects in Rodents*

Ms. Forouzan is a third year graduate student in Behavioral Neuroscience at University of Houston under supervision of Dr. Therese Kosten. Her long-term research interests involve understanding different aspects of behavioral and neurobiological mechanisms of substance use disorders and provide novel therapeutic treatments for drug addiction, primarily methamphetamine use disorder (AUD).

Her current research involves developing a new line of research to evaluate the role of the gut microbiome in methamphetamine use disorder using animal models.

Abstract:

Methamphetamine (MA) is one of the most frequently used amphetamine-type stimulants in the United States. Individuals who repeatedly abuse MA can develop MA use disorder (MuD)—a chronic, relapsing condition often triggered by withdrawal symptoms that develop following cessation of use. Long term abuse MA can result in negative health consequences including extreme weight loss, severe dental problems, malnutrition, anxiety, confusion, insomnia, mood disturbances, and violent behavior. Despite the well-documented dangers of chronic MA use, approximately 1.2 million people reported using MA in the past year. Given the lack of effective treatments for those with MuD, novel therapeutic targets must be considered. One potential target is the gut microbiome, which has an important influence on brain, behavior, and health as a part of the gut-brain axis. Therefore, the use of psychobiotics may provide a new way for treatments for drug addiction. In this study, we evaluated the effects of MA administration on withdrawal-induced behaviors and in the gut microbiota in female and male rats. These findings are preliminary, but provide direct evidence that administration of MA causes gut dysbiosis and withdrawal from chronic methamphetamine induce depressive-like but not anxiety-like behavioral effects in both female and male rodents. Our observation will contribute to a better understanding of the function of gut microbiota in the process of drug abuse.
Kyla Gibney, Predoctoral Student  
Cancer Center, MD Anderson Cancer Center  

*A Power Analysis for the Late Positive Potential (LPP): Optimizing Human Cue Reactivity Paradigms*

Kyla Gibney is a PhD student in the Neuroscience Graduate Program at the MD Anderson UT Health Graduate School of Biomedical Sciences. Kyla got her bachelor’s in neuroscience at Oberlin College where she worked in multisensory integration. Kyla works in neuroimaging with an interest in methods based research and in the cognitive and affective components of reward processing.

**Abstract:**
The Late Positive Potential (LPP) is an event-related potential (ERP) component that is reliably elicited by emotionally relevant stimuli, and it is frequently used in cue reactivity paradigms to assess electrophysiological responses to drug-related cues. The LPP could potentially be used for characterizing individual differences in reactivity to drug cues and predicting vulnerability to addiction and relapse. However, we do not know how many subjects per group and trials per subject are necessary to detect reliable LPP differences between two groups as a function of their magnitude. The goal of this study was to determine how these factors impact the statistical power of experiments investigating LPP group differences. Using ERP data previously collected in our laboratory, we conducted a Monte Carlo simulation of ERP experiments with varying numbers of subjects per group (10-100), numbers of trials per condition (5-40), and effect sizes between groups (0-2 µV). To simulate experiments, subsets of subjects were randomly sampled from the main dataset, and subsets of trials were then randomly sampled from each subject. Effects of known size were then added to or subtracted from the LPP of each group to create the desired between groups effect size. These simulations were then repeated 1,000 times per experiment. To test for between-subjects effects, one-way ANOVAs were conducted on each iteration of each experiment with group as factor. The percentages of F-values at or above the critical F value for each experiment were calculated to represent statistical power. As expected, statistical power is greater at greater numbers of subjects per group, greater numbers of trials per condition, and at larger effect sizes. Additionally, it was observed that power asymptotes to 100% starting at 30 subjects per group and 20 or more trials per condition only when effect sizes were of 1.5 µV or more. Our results suggest that for investigators studying group differences in the LPP of modest effect sizes (less than 1.5 µV, as often reported in the literature1–3) it is necessary to recruit at least 50 subjects or more per group and to include 30 trials or more per condition.
Ms. Merritt received a Bachelor of Science degree in psychology with a minor in biology at Virginia Commonwealth University, where my research career in addiction sciences began. This invaluable experience led me to pursue a Ph.D. in the Pharmacology and Toxicology program at the University of Texas Medical Branch, where she is currently training under the mentorship of Dr. Kathryn A. Cunningham at the Center for Addiction Research. Her research identifies neurobiological markers and behavioral phenotypes that predict individual differences in susceptibility to develop substance use disorders.

Abstract:
The limbic-corticostriatal circuit plays a complex and important role in impulsive action, or the inability to withhold a prepotent motor response, as demonstrated by lesion, reversible inactivation, and genetic manipulation. We employed next-generation sequencing as a discovery-based approach to investigate the unique transcriptomic profile associated with levels of impulsive action in male Sprague-Dawley rats. Low impulsive (LI) and high impulsive rats (HI) were defined by lower and upper quartiles of premature responses in the 1-CSRT task (n = 4-7/phenotype), respectively. Following behavioral phenotyping, we isolated the medial prefrontal cortex (mPFC) and processed mRNA for transcriptomic profiling. Interpretation of transcriptomic data was achieved using statistical gene-set enrichment methods in which differentially expressed genes are intersected with sets of genes that are associated with a particular biological function or pathway. Comparison analyses revealed expression of 612 transcripts in the mPFC of HI rats that were significantly higher or lower relative to LI rats. Employment of Panther Pathway and Protein Class Analysis identified several signaling networks with activity that was significantly higher (e.g., heterotrimeric G-protein signaling pathways) and lower (e.g., apoptosis signaling pathway) in the mPFC of HI, relative to LI, rats. We then employed Ingenuity Pathway Analysis to identify upstream transcriptional regulators. Predicted upstream regulators (Z-score > 2 and overlap p < 0.01) included growth factors and cytokines [e.g., tumor growth factor β1 (TGFβ1), Z=4.060, p=4.97e-13; brain-derived neurotrophic factor (BDNF), Z=2.693, p=2.6e-11] as well as transcription regulators [Specificity protein 1 (Sp1), Z=3.305, p=8.64e-7; catenin β1 (CTNNB1), Z=3.662, p=9.08e-6]. Interestingly, there were genes in our dataset previously reported to be regulated by cocaine (Z=2.254, p=2.40e-7) (e.g., Fos, Arc, and Egr2), although these subjects were not previously exposed to cocaine. We verified the expression profile of Egr2 in HI and LI rats through quantitative real-time polymerase chain reaction (RT-PCR) analyses and observed a positive correlation of Egr2 mRNA expression with premature responses (R2 = 0.29; p < 0.05). Thus, our tandem utilization of next-generation sequencing and pathway analyses identified a registry of candidate gene targets in the mPFC associated with impulsivity, including Egr2.
Dr. Versace’s current line of research focuses on investigating the neurobiological underpinnings of nicotine addiction and smoking behavior. His work aims at identifying new targets for treatment interventions, assessing treatment efficacy, evaluating risk of relapse, and improving clinical outcomes through patient-to-treatment matching. To achieve these goals, they use brain imaging techniques such as functional magnetic resonance imaging (fMRI) and dense sensor array event-related potentials (ERPs) to characterize the dysfunctional brain mechanisms that mediate reactivity to cigarette-related cues and natural rewards in smokers.

Abstract:
Progress in basic neuroscience has improved our understanding of addiction neurobiology, but what has proven difficult is translating this knowledge into effective relapse prevention treatments. In previous retrospective studies we showed that 1) smokers with larger brain responses to cigarette-related cues than pleasant stimuli (C>P) are more vulnerable to relapse than smokers with the opposite brain reactivity profile (P>C) and 2) when trying to quit, C>P smokers benefit from varenicline more than P>C smokers. The goal of this study was to show the feasibility of using this biomarker to prospectively assign P>C and C>P smokers to the smoking cessation treatment most likely to benefit them. We used a newly developed classification algorithm (For details, please see poster by Frank et al.) to identify on a subject-by-subject basis the P>C and C>P brain reactivity profiles in a group of 154 smokers interested in quitting. We used the neuroaffective classification information as a stratifier when we randomized smokers to either varenicline or nicotine patch. We assessed biochemically verified abstinence at the end of treatment (EOT, 10 weeks after the quit date), three, and six months after the quit date. The results confirmed that, when trying to quit, smokers with the C>P brain reactivity profile are more likely to benefit from varenicline than P>C smokers. The Bayesian analyses showed that the posterior probability of this effect was .96 at EOT, .75 at the three months follow up, and .96 at the six months follow-up. These results demonstrate that identifying the neurobiological mechanisms underlying relapse can contribute to the development of better targeted therapeutic interventions to prevent smoking relapse and improve treatment outcomes.

This work was supported by CPRIT award RP140262 to PMC and funds from the MD Anderson Moonshot program awarded to PMC.
Angela M. Heads, Ph.D. is Assistant Professor in the Department of Psychiatry and Behavioral Sciences at the University of Texas Health Science Center at Houston (UTHealth), McGovern Medical School. She is a licensed psychologist involved in addiction research and clinical service provision for substance use disorders and co-occurring psychiatric disorders. She is the Project Director for the UT-HEARTS program, a SAMHSA funded program providing substance use disorders treatment and HIV prevention services for underserved population. She is a New Connections Scholar through the Robert Wood Johnson Foundation conducting research on risk and protective factors in adolescence associated with substance use disorders in emerging adulthood. Her research interests also include HIV prevention, behavioral health disparities, and cultural determinants of mental and physical health in underserved populations.

Abstract:
Over 100 million surgical procedures were performed in the United States in 2010, with approximately 98.6% of these patients receiving opioids for post-surgery analgesia and pain management. The number of patients who go on to demonstrate chronic opioid use or misuse is not insignificant, with one study reporting up to 24%, depending on type of operation.1 Thus, the use of opioids in surgical patients is a particularly challenging problem that requires novel methods for managing pain while minimizing the risks of persistent opioid use after surgery.

At Memorial Hermann Hospital (MHH) in Houston post-injury patients typically receive opioids during hospitalization and a prescription for additional oral opioids at discharge. Currently, the trauma surgery unit at MHH lacks adequate care coordination to monitor patient progress after discharge. In an effort to bridge the gap between patients’ needs at discharge and aftercare clinic resources, a team of clinicians and investigators from MHH and the UTHealth Center for Neurobehavioral Research on Addiction (CNRA) have partnered to begin development of evidence-based treatment services for addressing pain and minimizing the risk of opioid pain medication misuse. This quality improvement project (QI) involves systematic collection of opioid risk data which will provide a critical needs assessment to inform the planning of subsequent intervention services for patients at MHH.

We report methods and preliminary analysis of this QI project involving the administration of the Opioid Risk Tool (ORT), a brief, self-report, validated screening tool designed to assess risk for continued opioid abuse among individuals prescribed opioids for treatment of chronic pain. The ORT, along with medical record review, is completed at a single time point during hospitalization, with follow up assessment of opioid medication use at post-discharge (2 and 4 weeks). Consecutive sampling is used to assess all eligible trauma patients seen on the trauma surgery unit at MHH over a six month period which is expected to yield a total sample size of approximately 900 patients in the 1 year duration of the project.
As of 10/31/2018, 107 ORT surveys were completed and available for preliminary analyses. The majority of participants were male (n=72, 67.3%). The mean ORT score was 2.94 (SD=4.07). Although males scored slightly higher (3.36) than females (2.09), these differences were not statistically significant. 74 participants (46 males) scored in the low risk range (score of 3 or lower on the ORT). 19 (15 males) scored in the medium risk range (4-7). 14 participants (11 males) scored in the high risk range (8 and above). Post discharge outcomes are also being captured via online survey, including: Percent of postsurgical trauma patients who continue to use opioid medications at 2 and 4 weeks post hospital discharge; and reported pain levels at 2 and 4 weeks post hospital discharge.

Results from this QI project will inform the development of improved hospital-based interventions for reducing risk of opioid misuse following surgery.

Gwyneth Ballentine, Digital Health Innovation Lead
TMC Innovation Institute

Inside the TMC Innovation Institute: Houston’s Home to Healthcare Startups

Gwyn is Digital Health Innovation Lead at the TMC Innovation Institute and works primarily with the TMCx accelerator and Biodesign programs to support and guide current and future companies toward commercial success with their innovative health care products. She also leads engagement of investors with the startup health care companies, as well as with TMC Innovation as a whole. Gwyn comes to TMC from Diversigen, a Baylor College of Medicine startup company, where she was the director of scientific operations and commercial development. While there, she worked with customers to design and manage projects for optimal results and played a leadership role in identifying strategic opportunities and partnerships that would advance their competitive position in the market. Gwyn has also worked with other startups across various R&D areas, including development of a novel treatment for antibiotic resistant bacterial infections and vaccine development for mosquito borne diseases, where she was successful in raising over $5 million in early stage-funding.

She holds an undergraduate degree in biochemistry from North Carolina State University, and an MBA and a Ph.D. in molecular pathology from Wake Forest University.

She is passionate about startups and the entrepreneurial environment and is eager to commercialize novel technologies in health care.
Thomas R. Kosten, MD, is the JH Waggoner Chair and Professor of Psychiatry, Pharmacology, Immunology, Pathology and Neuroscience, Director of the Division of Substance Use Addictions, and Emeritus Director of the Dan Duncan Institute for Clinical and Translational Research at Baylor College of Medicine. His other key appointments are Distinguished Professor of Psychiatry at Peking University Medical School and Adjunct Professor of Epidemiology and Behavioral Health at MD Anderson Cancer Center. He is a former Professor at Yale University School of Medicine, the founding Vice Chair for Addiction Psychiatry of the American Board of Psychiatry and Neurology, and Past President of both the American Academy of Addiction Psychiatry and the College on Problems of Drug Dependence. He is a Distinguished Life Fellow in the American Psychiatric Association (APA) and a Fellow of the American College of Neuropsychopharmacology (ACNP). He has served as a Congressional Fellow in the US House of Representatives and is a long-standing member of various commissions with the National Academy of Sciences (NAS), the Food and Drug Administration (FDA), the Federal Trade Commission (FTC), and the Department of Defense (DoD) primarily related to veteran health and drug safety and risk management. He is the current Editor for the American Journal on Addictions, and has over 750 publications on pharmacotherapy for addictions supported by over 50 grants from NIH, VA, DoD and various foundations in the USA and China. Dr. Kosten has been named “Top Doc” in the field of Psychiatry, rated among the top 10%, of physicians in Addictions Medicine, and in the top 1%, of U.S. physicians nationwide.

Abstract:
Dr. Kosten’s talk will focus on the cocaine vaccine that progressed to an FDA Phase 3 clinical trial. He will review the composition and mechanism of action for this vaccine and then cover the human outpatient clinical trials. These trials included both human laboratory tests examining this vaccine’s ability to block cocaine’s reinforcing effects and placebo controlled randomized clinical trials examining this vaccine’s ability to reduce outpatient cocaine use based on urine toxicology results. Finally, we found that a genetic variant in the coding for the enzyme dopamine beta hydroxylase could predict the vaccine’s ability to reduce cocaine use.
Jokūbas Žiburkus, Associate Professor
Biology and Biochemistry
University of Houston
*Phytocannabinoids and the Global Paradigm Shift*

The long-term goal of Dr. Jokūbas Žiburkus’ laboratory research is to understand the mechanisms of neuronal interactions in health and disease and to devise novel and alternative therapeutic treatments for untreatable neurological disorders. The lab employs a multi-disciplinary approach that synthesizes in vitro neurophysiology, neuropharmacology, imaging, molecular biology, immunohistochemistry, and computational neuroscience. Using these techniques, Žiburkus is trying to understand alterations in single neurons and neural networks that lead to epileptic seizures, abnormal excitability in Alzheimer’s disease, or occur following a traumatic brain injury. His lab has filed and continue developing patents for novel and combinatorial medications to treat neurological disorders, stroke, and even cancer. Recent work has focused on Dravet syndrome – a severe form of childhood epilepsy that is very hard to treat. Žiburkus is investigating how purines affect mortality, seizures, and other behavioral comorbidities in a transgenic mouse model of Dravet syndrome. He is also investigating other alternative compounds and their combinations for treatment of brain and heart hyperexcitability, seizure activity, and even cancer.

John Mendelson, Founder and Medical Director
Ria Health
*Can Tech Treat Alcoholism – The Ria Technologically Enabled AUD Treatment Solution*

Joh Mendelson MD is an Internists and Clinical Pharmacologist. He is a Senior Research Scientist at the Friends Research Institute and is the Founder of Ria Health. He has an active clinical practice, performs NIH-funded clinical research and is now a company Founder. Ria Health treats AUD using a telehealth platform deployed through a dedicated smart phone app that integrates twice daily breathalyzer measures, medication management, coaching and social supports. Ria is now available to ~49% of the US population and is scaling nationally. Mendelson will discuss the journey from academic and clinical physician to entrepreneur and present data on the efficacy of the Ria platform.

Abstract:
Dr. Mendelson will discuss alcohol and addictive disorders from Genesis to Google. He will present addiction myths, epidemiological sources and review alcohol consequences, treatments and end with a look at Ria Health and how technology is transforming addiction treatment.
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A Meta-Analysis of Regional Differences in White Matter Integrity in Stimulant Use Disorders

Beard CL¹, Schmitz JM¹, Lane SD¹, Soder HE¹, Suchting R¹, Yoon JH¹

¹Center for Neurobehavioral Research on Addiction, University of Texas Health Science Center at Houston

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ABSTRACT

Cocaine and methamphetamine are the two most commonly abused psychostimulants with long-term addiction associated with significant brain changes. Specifically, diffusion tensor imaging (DTI) studies have identified regional changes in white matter (WM) integrity in patients with stimulant use disorders compared to non-addicted subjects. We conducted the first meta-analytic review of DTI-based WM integrity in regions of interest of the corpus callosum and association fiber tracts, following PRISMA guidelines. Inclusion and exclusion criteria were determined by the authors in order to best capture WM integrity in individuals with primary stimulant use (i.e., cocaine and methamphetamine use disorders) in comparison to healthy control subjects. Twelve studies that focused on ROI-based analysis of WM integrity were extracted from an initial pool of 115 independent studies. Significantly lower fractional anisotropy (FA) values were evident in patient groups compared to controls, with a moderate overall effect (Hedges’ $g = -0.53$, 95% CI [-0.79, -0.26]). Available data for diffusion eigenvalues were also analyzed, revealing a significant effect for radial diffusivity (RD; $g = 0.24$, 95% CI [0.01, 0.45]), but not axial diffusivity (AD; $g = 0.35$, 95% CI [-0.25, 0.95]), or mean diffusivity (MD; $g = 0.20$, 95% CI [-0.01, 0.41]). Subgroup analyses were explored including specific regions of interest, primary substance use (cocaine or methamphetamine), poly-substance use, and imaging technology. Results suggest a consistent effect of compromised white matter integrity for individuals with stimulant use disorder and raise the interesting possibility of testing neuroprotective agents to improve WM integrity as part of treatment.
Role of Medial Prefrontal Cortex NMDA Receptors in Inherent Impulsivity.
Davis-Reyes, BD1, Campbell, VM1, Chapman, HL1, Stafford, S1 and Anastasio, NC1,2
1Center for Addiction Research, 2Dept Pharm & Tox, UTMB, Galveston, TX USA.

Impulsivity, broadly defined as behavior without sufficient forethought, is a multifaceted behavioral manifestation that has implications in several disorders including addiction, schizophrenia, and obesity. Glutamate neurotransmission in the medial prefrontal cortex (mPFC), an important brain region in decision-making and goal-oriented behaviors, has implications in inherent impulsivity. The N-methyl-D-aspartate receptors (NMDARs) are glutamate receptors that are localized throughout the brain, including the mPFC. Functional receptors are heterotetramers composed of at least two NMDAR1 (GluN1) subunits and two NMDAR2 (GluN2A-D). Localization of these receptors within the synapse plays an important functional role within the mPFC. GluN2A-containing NMDAR are predominantly found in the synapse, while GluN2B-containing NMDAR are primarily localized extrasynaptically. Here, we tested the hypothesis that individual differences in impulsivity are driven by the composition of the NMDAR complex, specifically the expression and localization of the NMDAR subunits, within the mPFC. Outbred male Sprague Dawley rats were identified as high (HI) or low (LI) impulsive using the one-choice serial reaction time (1-CSRT) task; the upper and lower quartile of animals were identified as HI or LI rats, respectively. Following phenotypic identification, mPFC synaptosomal protein was extracted from HI and LI rats to assess the composition of the NMDAR complex via immunoblot and/or immunoprecipitation techniques. Synaptic localization was investigated by immunoprecipitation for postsynaptic density 95 (PSD95) with subsequent western blotting for GluN2A and GluN2B. Performance on the 1-CSRT task was rapidly acquired and the HI/LI phenotype was stably expressed across training. HI rats had lower mPFC GluN1 and GluN2A, but higher GluN2B synaptosomal protein expression (p<0.05) vs LI rats. Further, levels of pGluN2B were also higher in HI vs LI rats (p<0.05). Co-immunoprecipitation analyses indicate a higher GluN2B:PSD95 synaptosomal protein complex in HI vs LI rats (p<0.05). Thus, there is a possible transformation of the mPFC NMDAR complex composition and/or synaptic localization that may underlie high inherent motor impulsivity. Increased understanding of the complex regulation of NMDAR balance within the mPFC as it relates to individual differences in impulsivity may lead to a better understanding of risk factors and treatments for several neurological disorders, including addiction.

Financial Support: R00 DA033734; T32 DA07287
Pioglitazone Alters White Matter Integrity In A Rodent Model Of Cocaine Use Disorder

Dimet, Andrea L1; Denner, Larry A2; Miller, William R3; Cunningham, Kathryn A4; Huentelman, Matthew J5; Lane, Scott D6 and Dineley, Kelly T7
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Cocaine use disorder (CUD) causes structural and functional changes in white matter (WM) and gray matter (GM) structures which drive behavioral phenotypes, one of which is cocaine-seeking behavior. Rodent models recapitulate the structural changes, and cocaine-seeking can be measured by training rats to self-administer (SA) cocaine in association with discrete and contextual cues, placing them into forced abstinence (FA), then measuring their responsiveness to the cocaine-paired cues following FA (cocaine cue reactivity). We discovered that the FDA-approved peroxisome proliferator-activated receptor gamma (PPARγ) agonist pioglitazone (PIO, ActosTM) attenuates cocaine cue reactivity in rats when PIO is administered during FA. Importantly, this effect of PIO is reversed by pretreatment with the PPARγ antagonist GW9662, thus it is a PPARγ-specific effect. Phosphorylated extracellular signal-regulated kinase (pERK) is a protein we identified in complex with PPARγ, and thus a potential co-regulator. We hypothesize that PPARγ agonism counteracts the cocaine-mediated alterations in WM and GM underlying persistent cocaine-seeking behavior through the induction of markers for functional and structural integrity via downstream transcriptional or pERK-related mechanisms. The objectives of the current study were three-fold: 1) Identify genes regulated by PPARγ agonism in the model, and determine if particular response elements drive the transcriptional landscape, 2) Determine if the expression of particular proteins changes with PPARγ agonism, and 3) Elucidate if the WM integrity of tracts of interest changes with PPARγ agonism.

Our methods included RNA sequencing and analysis, protein expression analyses with the Protein Simple Wes™, and Luxol Fast Blue staining. Brain regions studied included the hippocampus (HIP), prefrontal cortex (PFC), caudate/putamen, internal capsule, fimbria, and corpus callosum (CC). Our results indicated that the overall PIO-regulated transcriptional landscape is not driven by the response elements we expected. However, PIO regulated pathways important to cell death and inflammation, which were enriched for PPAR and ERK-related response element-containing genes in the PFC. Additionally, PIO increased the expression of a water channel, aquaporin 4, (AQP4) and decreased the expression of an essential component of myelin, proteolipid protein 1 (PLP1), in the HIP of cocaine SA rats. Finally, we identified tracts of interest changed by cocaine SA and PIO, and the medial anterior CC stood out as a target demonstrating increased WM staining with PIO treatment. In conclusion, our work reveals 1) PIO alters gene expression in pathways important to cell death that are enriched for PPAR and ERK-related genes in the PFC, 2) PIO changes protein expression in the HIP suggestive of WM restructuring, and 3) PIO increases WM in the medial anterior CC, which recapitulates findings using diffusion tensor imaging in human CUD subjects taking PIO. Funding and resources were provided by the NIEHS Training Program (T32ES007254) and Peter F. McManus Charitable Trust, as well as UTMB’s Center for Addiction Research, Mitchell Center for Neurodegenerative Diseases, Institute for Translational Sciences, and Rodent In Vivo Assessment Core.
The Ventral Tegmental Area and Methylphenidate (Ritalin) Addiction in the Rat Model

Floren S¹, King N¹, Carrasco A¹, Dafny N¹
¹. Department of Neurobiology and Anatomy, McGovern Medical School, Houston, TX

Corresponding author: Samuel Floren, Department of Neurobiology and Anatomy, McGovern Medical School, 6431 Fannin St, Houston, TX, 77030, E-mail: Samuel.a.floren@uth.tmc.edu. Methylphenidate (MPD) is a central nervous psychostimulant that has long been the treatment of choice in behavioral disorders such as attention deficit/hyperactivity disorder (ADHD) and narcolepsy in both children and adults. However, its abuse by healthy subjects as a “study drug” and “recreational drug” is on the rise. This generates an incentive to know the neuroanatomic location where it exerts its effect. The areas of the brain that play a role in the response to psychostimulants are known as the neural system. The ventral tegmental area (VTA) is a major source of dopamine (DA) to the brain that is part of the neural system, and MPD is considered an indirect DA agonist. The objective of this study is to investigate role of the VTA in acute and chronic MPD exposure. To explore this, behavioral recordings were made of rats before and following acute and chronic MPD treatment following five different VTA lesion types: intact, sham surgery, nonspecific bilateral electrolytic lesion, glutaminergic specific chemical lesion (using injection of ibotenic acid), and dopaminergic specific chemical lesion (using injection of 6-hydroxydopamine). Each group had baseline recordings made followed by surgeries to introduce the appropriate lesions. They were give six recovery days to establish a new baseline, followed by six consecutive days of MPD administration. This was followed by a three day washout period and administration of a re-challenge of MPD. Comparisons between select experimental days were then performed to analyze the lesions’ effect on the change in baseline, the acute effect of MPD, and the induction and expression phase of the chronic effect of MPD. The results indicate that the glutaminergic synapses of the ventral tegmental area play a significant role in the acute effect of MPD, and its dopaminergic synapses are essential to both the acute and chronic MPD effects.
The Caudate Nucleus’ Role in Methylphenidate (Ritalin) Pharmacotherapy

King N1, Floren S1, Thomas M1, Dafny N1

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Corresponding author: Samuel Floren, Department of Neurobiology and Anatomy, McGovern Medical School, 6431 Fannin St, Houston, TX, 77030, E-mail: Samuel.a.floren@uth.tmc.edu. Methylphenidate (MPD) is the most widely prescribed psychostimulant for the treatment of attention deficit hyperactivity disorder (ADHD), and is growing in use as recreational drug or academic enhancer. MPD acts on the motive and motor circuits to produce its effects on behavior. The caudate nucleus (CN) is known to be a part of the motive and motor circuits, hence this study focuses on the role of the CN in response to acute and chronic MPD exposure. Five groups of rats were used: control (n=8), sham CN lesion (n=8), non-specific electrolytic CN lesion (n=8), dopaminergic-specific by 6-OHDA toxin CN lesion (n=8), and glutaminergic-specific by ibotenic acid toxin CN lesion (n=8); lesions were placed bilaterally. On experimental day (ED) 1, all groups received a saline injection. On ED 2 or 3, surgeries took place and rats were allowed to recover for 4 days (ED 3-7). Rats received six daily MPD 2.5 mg/kg injections (ED 9-14), three days of washout with no injection (ED 15-17), followed by a re-challenge with MPD 2.5 mg/kg (ED 18). Locomotive activity was recorded immediately after each injection for 60 minutes by a computerized animal activity monitor, i.e. the open field assay. The electrolytic CN lesion group responded to MPD acute and chronic exposure similarly to the control and sham groups. The dopaminergic-specific 6-OHDA CN lesion group failed to respond to MPD exposure both acute and chronically. The glutaminergic-specific ibotenic acid CN lesion group responded to MPD exposure acutely but failed to respond to chronic MPD exposure. The dopaminergic system of the CN is necessary for MPD to manifest acute and chronic effects on behavior. The glutaminergic system within the CN is essential for the chronic effects of MPD. Thus, the CN plays a significant role in the expression of acute and chronic MPD exposure’s effects on behavior.

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². Department of Psychology, University of Houston

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Methamphetamine (MA) is one of the most frequently used amphetamine-type stimulants in the United States. Individuals who repeatedly abuse MA can develop MA use disorder (MuD)—a chronic, relapsing condition often triggered by withdrawal symptoms that develop following cessation of use. Long term abuse MA can result in negative health consequences including extreme weight loss, severe dental problems, malnutrition, anxiety, confusion, insomnia, mood disturbances, and violent behavior. Despite the well-documented dangers of chronic MA use, approximately 1.2 million people reported using MA in the past year. Given the lack of effective treatments for those with MuD, novel therapeutic targets must be considered. One potential target is the gut microbiome, which has an important influence on brain, behavior, and health as a part of the gut-brain axis. Therefore, the use of psychobiotics may provide a new way for treatments for drug addiction. In this study, we evaluated the effects of MA administration on withdrawal-induced behaviors and in the gut microbiota in female and male rats. These findings are preliminary, but provide direct evidence that administration of MA causes gut dysbiosis and withdrawal from chronic methamphetamine induce depressive-like but not anxiety-like behavioral effects in both female and male rodents. Our observation will contribute to a better understanding of the function of gut microbiota in the process of drug abuse.
Identifying Smokers At Higher Risk For Relapse: Validation Of A Neuroimaging-based Classification Algorithm

David W. Frank\(^1\), Menton Deweese\(^2\), and Francesco Versace\(^1\)

\(^1\) Department of Behavioral Science, UT MD Anderson Cancer Center
\(^2\) Department of Teaching and Learning, Peabody College at Vanderbilt University

Corresponding Author: David Frank, Department of Behavioral Science, UT MD Anderson Cancer Center, 1155 Pressler St., Houston, Texas, dfrank@mdanderson.org

Progress in basic neuroscience has improved our understanding of addiction neurobiology, but what has proven difficult is translating this knowledge into effective relapse prevention treatments (Everitt, 2014). Recently, we reported that smokers with larger neuroaffective responses to cigarette-related cues compared to pleasant stimuli ("C>P") are more likely to relapse than smokers with the opposite brain reactivity profile ("P>C"). We hypothesized that this neurobiological marker could be used to identify smokers with high vulnerability to relapse. The goal of this study was to 1) build a classification algorithm to identify, on a case by case basis, smokers characterized by the P>C or the C>P ERP profiles, and 2) validate the clinical relevance of this classification algorithm in an independent dataset where we assessed smoking abstinence during a quit attempt in smokers classified as P>C or C>P. To build the classification algorithm, we applied discriminant function analysis on the dataset where we originally observed the significant association between smoking abstinence and neural reactivity to emotional stimuli. We confirmed the predictive validity of the classification algorithm on an independent data set that included new data from 177 smokers interested in quitting. For each participant we collected ERPs to emotional images before the quit attempt and we assessed smoking abstinence 12 months after the quit attempt. Using brain responses, the algorithm classified 111 smokers as P>C and 66 as C>P. The overall low abstinence rate notwithstanding (8.5% of the sample achieved CO verified 12 months abstinence), individuals classified as P>C were 2.5 times more likely to be abstinent than smokers classified as C>P (12% vs. 4.8%). These results suggest that neuroimaging techniques can help advance our knowledge of the neurobiological underpinnings of nicotine addiction and improve clinical applications.

This work was supported by the National Institute on Drug Abuse under awards R01-DA032581 and R21-DA038001 to Francesco Versace.
Peripheral Methylome Analysis in Cocaine Use Disorder Patients Suggests Brain-Relevant Alterations in the Innate Immune System

Fries GR\textsuperscript{1}, Viola TW\textsuperscript{2}, Sanvicente-Vieira B\textsuperscript{2}, Rovaris DL\textsuperscript{3}, Bau CD\textsuperscript{3}, Schmitz J\textsuperscript{1}, Walss-Bass C\textsuperscript{1}, Grassi-Oliveira R\textsuperscript{2}

1. Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston (UTHealth)
2. Brain Institute of Rio Grande do Sul (InsCer), Pontifical Catholic University of Rio Grande do Sul (PUCRS), Brazil.
3. Department of Genetics, Universidade Federal do Rio Grande do Sul (UFRGS), Brazil

Corresponding author: Gabriel R. Fries, Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, 1941 East Rd, 77054, Houston, TX, E-mail: Gabriel.R.Fries@uth.tmc.edu

Recent studies have implicated a role for DNA methylation in modulating addictive behavior. However, previous reports have failed to identify robust brain-relevant alterations in periphery, which has limited functional studies with genes of interest. In this study, we aimed to investigate blood methylome alterations in patients with cocaine use disorder (CUD), compared to controls, and explore their relevance to brain tissue. Genome-wide methylation was assessed in blood from 99 patients with CUD and 90 controls matched by age, sex, and ethnicity. Assessments were made using the Infinium MethylationEPIC BeadChip (Illumina) and analyzed by the RnBeads package. Comparisons between groups were made for CpGs and region levels controlling for age, sex, BeadChip, batch, and blood cell type composition, with adjustment for false discovery rate (FDR). Groups showed a significant FDR-corrected (p<0.05) difference in methylation of 34 genes. Of these genes, S100A8 was found by gene set enrichment analyses to be involved in several pathways related to the innate immune system. S100A8, a toll-like receptor 4 (TLR4) agonist, was identified as one of the primary differentially expressed genes in the PFC and striatum of rats treated with stimulants amphetamine and methamphetamine. TLR4 antagonists are currently being used in treatment of alcohol and opioid dependence. We are in the process of analyzing additional peripheral samples from our cohort, together with postmortem brain tissue. Our current findings support a role of the TLR4 and innate immune system pathways in cocaine addiction, and may be helpful in future development of novel treatments for addiction.

Funding sources: 1R01 DA 044859-01 (National Institute on Drug Abuse).
Growth Hormone Secretagogue Receptor 1α (GHSR1α) Antagonism Differentially Impacts Cocaine Intake and Cue Reactivity in Male Rats

Garcia, E.J.1, Brehm, V.D.1, Fox, R.G.1, Anastasio, N.C.1,2, & Cunningham, K.A.1,2

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Ghrelin is the endogenous ligand for the growth hormone secretagogue receptor 1 alpha (GHSR1α), a G-protein-coupled-receptor (GPCR) distributed within nodes of the mesolimbic reward circuit. Ghrelin administration increased cocaine-induced hyperactivity and plasma ghrelin correlated with the magnitude of cocaine-seeking, while blockade of GHSR1α suppressed cocaine-evoked behaviors in rodents. Here, we tested the hypothesis that the GHSR1α antagonist JMV2959 (JMV) will suppress cocaine intake during self-administration (SA) or lever presses for cocaine-associated cues during abstinence (cue reactivity). Male Sprague-Dawley rats were trained to stability on cocaine self-administration (0.25 mg/kg/0.1 ml/infusion) prior to assessment of intraperitoneal (i.p) injection of 0.5, 1 or 2 mg/kg of JMV or saline (0.9%) administered 20 min before the SA session in a within-subjects design. A second cohort of rats was trained to stability on an FR5 schedule of cocaine SA (0.75 mg/kg/0.1 ml/infusion) in daily 180-min sessions. Twenty-four hours after the last cocaine SA session, rats were injected with JMV (1 or 2 mg/kg; i.p.) or saline 20 min before the cue reactivity test during which presses on the previously active lever resulted in delivery of cocaine-associated cues, but not cocaine. Pretreatment with JMV did not suppress cocaine intake nor alter inactive lever presses at any dose tested. Pretreatment with JMV suppressed cocaine cue reactivity at 2 mg/kg; no JMV effects were observed on inactive lever responses. Time course evaluations of the cue reactivity test session revealed a significant suppression of lever presses for cocaine-associated cues during the last 40 min of the 60 min session following pretreatment with 2 mg/kg of JMV (p < 0.05). These results indicate that the GHSR1α antagonist JMV differentially impacts the drive to seek, but not take, cocaine. Given that cue reactivity (attentional bias toward cocaine-associated cues) is a key phenotype that sets up vulnerability to relapse during recovery, future studies will investigate the neurocircuity through which GHSR1α systems regulate this facet of relapse vulnerability in cocaine use disorder.

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The Late Positive Potential (LPP) is an event-related potential (ERP) component that is reliably elicited by emotionally relevant stimuli, and it is frequently used in cue reactivity paradigms to assess electrophysiological responses to drug-related cues. The LPP could potentially be used for characterizing individual differences in reactivity to drug cues and predicting vulnerability to addiction and relapse. However, we do not know how many subjects per group and trials per subject are necessary to detect reliable LPP differences between two groups as a function of their magnitude. The goal of this study was to determine how these factors impact the statistical power of experiments investigating LPP group differences. Using ERP data previously collected in our laboratory, we conducted a Monte Carlo simulation of ERP experiments with varying numbers of subjects per group (10-100), numbers of trials per condition (5-40), and effect sizes between groups (0-2 µV). To simulate experiments, subsets of subjects were randomly sampled from the main dataset, and subsets of trials were then randomly sampled from each subject. Effects of known size were then added to or subtracted from the LPP of each group to create the desired between groups effect size. These simulations were then repeated 1,000 times per experiment. To test for between-subjects effects, one-way ANOVAs were conducted on each iteration of each experiment with group as factor. The percentages of F-values at or above the critical F value for each experiment were calculated to represent statistical power. As expected, statistical power is greater at greater numbers of subjects per group, greater numbers of trials per condition, and at larger effect sizes. Additionally, it was observed that power asymptotes to 100% starting at 30 subjects per group and 20 or more trials per condition only when effect sizes were of 1.5 µV or more. Our results suggest that for investigators studying group differences in the LPP of modest effect sizes (less than 1.5 µV, as often reported in the literature1–3) it is necessary to recruit at least 50 subjects or more per group and to include 30 trials or more per condition.

Novel Strategies for the Treatment of Opioid Use Disorder: Anti-Fentanyl Vaccine

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Corresponding author: Dr. Colin N. Haile, Department of Psychology, University of Houston, Health 1, 4849 Calhoun Rd Room 436, Houston, TX, E-mail: cnhaile@uh.edu. The latest statistics for the USA indicate an alarming increase in overdose deaths in 2017 with nearly 50,000 of those deaths involving opioids. A significant number of these deaths can be attributed to the availability of inexpensive and highly potent opioids such as fentanyl (FEN). FEN is also associated with increased rates of opioid use disorder (OUD). Available pharmacotherapies unfortunately have not proven suitable therefore new approaches are needed. A novel treatment strategy to avert potential overdose and relapse in individuals with OUD attempting to cease opioid use is vaccination with an anti-FEN vaccine. In our previous work, we generated a vaccine against methamphetamine (METH; tetanus toxoid linked to succinyl-METH) that produced anti-METH antibodies. Experiments combining our vaccine with the adjuvant Alum (aluminum hydroxide), and the TLR5 (toll-like receptor) agonist entolimod, significantly increased the antigenic potency of the vaccine. In the present series of studies we apply this same approach in the development of an anti-fentanyl vaccine.

Objectives: Our primary objectives were to 1) produce an anti-fentanyl vaccine and assess whether the vaccine would elicit fentanyl-specific antibodies and 2) determine fentanyl’s analgesic effects in vaccinated and non-vaccinated mice. Methods: A FEN hapten (glutaryl-FEN) was generated by first attaching a glutaryl linker to N-phenyl-1-(2-phenylethyl)-4-piperidinamine. Then the terminal carboxylic acid was conjugated via 1-ethyl-3-(3-dimethyl-aminopropyl) carbodiimide (EDC)/sulfo-N-hydroxysuccinimide (Sulfo-NHS) amide formation to the immunogenic TT carrier protein. The resulting conjugate (TT-FEN, 8µg) was combined with Alum (1500µg) and entolimod (1µg) and incubated at 4 C° overnight. Mice (Balb/c, female) were then vaccinated at 0, 3 and 6 weeks and blood samples taken at 6, 8 and 12 weeks and concentrations of anti-fentanyl antibodies quantitated using a customized ELISA. Analgesic effects of fentanyl (1.0mg/kg, IP) were determined using the tail flick (Ugo Basil) assay. Results: Anti-fentanyl antibodies were detected at 6, 8 and 12 weeks post-vaccination with the highest levels seen at the latter time point. Significant main effects for drug (fentanyl vs saline, p<0.007) and vaccine (no vaccine vs vaccine, p=0.03) were found in addition to a significant drug x vaccine interaction (p=0.003) for data produced from the tail flick assay. Post hoc analysis showed that fentanyl significantly increased latency to tail flick in non-vaccinated mice (p<0.001) but not in vaccinated mice (p=0.83) and this effect was significantly different between groups (p<0.001).

Conclusions: Results indicate our vaccine can generate anti-fentanyl specific antibodies and significantly attenuate the analgesic effects of fentanyl. Future studies will assess the impact of this vaccine on the reinforcing effects of fentanyl. Funding Source: Kadvax Technologies Inc.
Novel Serotonin (5-HT) 5-HT2 Receptor Neuroprobes Exhibit Unique Pharmacological Properties

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The 5-HT2A receptor (5-HT2AR) and 5-HT2CR are G protein-coupled receptors (GPCRs) implicated in the regulation of normal function (e.g., satiety, sleep) and in facets of neuropsychiatric disorders (e.g., addiction, schizophrenia). The main functional GPCR unit for the 5-HT2AR and 5-HT2CR is proposed to be their homomeric form, and recent evidence supports the formation of 5-HT2AR:5-HT2CR heteromeric complexes, presenting prospects for novel ligands for these receptor assemblies. Given that the selective 5-HT2AR antagonist M100907 (M) and the 5-HT2CR agonist WAY163909 (W) each suppress motor impulsivity and cocaine-evoked behaviors, and low doses of M100907 plus WAY163909 synergize, we synthesized homomeric (M-M) and heteromeric (M-W) ligands through a tether linkage using click chemistry methods. As the length of the tether attached to parent pharmacophores increased (6-24 atoms), the molecules exhibited novel pharmacological profiles in vitro. We templated a bivalent compound by tethering M100907 to M100907 with the 12 atom tether (M-12-M) and this bivalent retained efficacy to suppress cocaine-induced hyperactivity, without alteration of spontaneous activity. Heterobivalent ligands with desired pharmacological properties were synthesized (14 atom linker, M-14-W+; 17 atom linker, M-17-W+ or M-17-W5,5; 20 atom linker, M-20-W+) from corresponding monovalent derivatives. M-17-W+ (1 mg/kg, ip) did not suppress spontaneous or cocaine-evoked (15 mg/kg, ip) locomotor activity. M-17-W5,5 (5 mg/kg,ip) suppressed total horizontal ambulation; however, the heterobivalent did not alter cocaine-evoked locomotor activity. Excitingly, M-17-W5,5 (2 mg/kg) significantly suppressed motor impulsivity in the one-choice serial reaction time task. Novel M100907:M100907 homobivalent and M100907:WAY163909 heterobivalent molecules have distinct activities in vitro and in vivo. Given our new knowledge of a 5-HT2AR:5-HT2CR heterocomplex, we propose to optimize the tether length of molecules and explore the bivalents to elucidate the structural and functional source of activity.

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The Impact of Psychiatric Disorders on The Ability to Quit Smoking: A Case Control Cohort

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Background
Smokers are more likely to have a psychiatric disorder than are non-smokers and conversely, individuals with a psychiatric disorder are almost twice as likely to be smokers as individuals without a psychiatric disorder. As a group, smokers with psychiatric disorders consume a disproportionate number of cigarettes and some data show that smokers with psychiatric disorders are less likely to quit smoking than are other. These observations raise questions about whether psychiatric disorders are associated with the severity of tobacco dependence and the ability to quit. On the other hand if treating psychiatric disorders.

Objective
The present research is intended to examine the relationship of psychiatric disorders to tobacco dependence and cessation outcomes.

Methods
A case-control study using data collected routinely in a Tobacco Treatment Program at a large cancer hospital. From patients who were referred to and got evaluated by the program psychiatrist (N = 503, 61.8% women), 48.7% were diagnosed with MDD, 39.8% with Insomnia, 33% with Anxiety, 6% with PTSD and 3.6% with Panic Disorder. Psychiatric disorders were diagnosed, treated and followed up by the same psychiatrist during treatment for tobacco cessation. Self-reports of patients' abstinence were obtained independently by program staff calls, at 3, 6 and 9 months from consultation.

Results
Preliminary analyses showed that depressed patients had lower abstinence rates in general compared to non-depressed patients at EOT, 6 months and 9 months.
Depressed patients who were treated for depression had higher abstinence rates than did those who were not treated for depression.
Comparing smokers with depression who were not treated for depression vs. those who were treated, the latter had higher abstinence rates at 9 months (p-value = 0.035

Conclusions
Information on current or lifetime psychiatric disorders may help clinicians gauge the severity of tobacco dependence, the ability to quit and relapse risk. These findings also illustrate the importance of using standardized tobacco dependence and mental health assessments.
Real-Time Audio/Video Versus In-Person Treatment for Smoking

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Background:
Tobacco use (smoking) is the leading cause of preventable disease, disability, and death in the United States and around the world. Audio/Video (A/V) conferencing has been successfully used to deliver smoking cessation interventions as well as other psychiatric and medical services.

Objective:
In this study, we look at whether real time A/V evaluation and treatment planning for smoking cessation is as effective as the same if provided in-person.

Methods:
At total of 4779 Tobacco Treatment Program patient evaluations (in-person at the main campus or via real-time A/V to satellite clinics). Self-reports of patients’ smoking abstinence were obtained by phone follow-up, by non-clinical program staff at 3, 6, and 9 months, from the date of initial consultation.

Results:
Among the 4779 patients, 4481 (93.8%) of the evaluations were done in-person and 298 (6.2%) via A/V at one of three satellite clinics, with over 90% of the follow-ups were done by phone for both groups. The abstinence rate in the two groups did not show a significant difference at 3 months (p=0.172), at 6 months (p=0.171), or at 9 months (p=0.54). Other variables such as years of smoking, FTND and CO were similar while depression and anxiety scores were found to be higher among main campus patients.

Conclusions:
Offering tobacco evaluation and treatment planning via A/V seems to result in similar quit rates as providing it in-person.

Summary:
Real-time A/V has the potential to bridge a big gap in the delivery of health care and facilitate the provision of highly subspecialized care from academic medical centers to any remote location.
Cys23Ser Single Nucleotide Polymorphism Alters Function and Localization of the Serotonin 2C Receptor (5-HT2C R) In Vitro

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The application of pharmacogenetics provides an opportunity to greatly improve treatment outcome by identifying potential biomarkers to facilitate the development of personalized pharmacotherapies for cocaine use disorder. A non-synonymous SNP of the human 5-HT2C R gene that converts a cysteine (Cys) to a serine (Ser) at amino acid codon 23 (Cys23Ser) appears to impact 5-HT2C R pharmacology at a cellular and systems level. The Cys23Ser SNP has been linked to changes in efficacy of psychiatric therapeutics and clinically to several psychiatric disorders and related behaviors, including impulsivity and cocaine cue reactivity, and thus may serve as a biomarker for cocaine use disorder-related behaviors. While the functional impact of this SNP is not well understood, overall the Ser23 variant could impact behavioral and pharmacological responses, possibly due to reduced function and a distinct subcellular localization profile. The ultimate level of 5-HT2C R functionality is determined by a culmination of factors, such as effective coupling to/activation of intracellular signaling components and trafficking/endosomal recycling. We hypothesized that the Cys23Ser SNP alters 5-HT2C R intracellular signaling via changes in receptor subcellular localization in vitro. We generated CHOp38 cell lines stably expressing the Cys23 or Ser23 variant. 5-HT evoked a concentration-related Ca²⁺ release in the Cys23 (EC₅₀=0.58 nM) and the Ser23 (EC₅₀ 2.29 nM) cell lines. The Ser23 variant demonstrated 43% lower maximum 5-HT-induced Ca²⁺ release and a rightward shift in potency vs the Cys23 variant (p<0.05). Western blot and immunocytochemistry results show lower 5-HT2C R plasma membrane expression in the Ser23 vs the Cys23 cell lines (p<0.05); no differences in total protein expression between the Cys23 or Ser23 variant was detected. Subcellular localization studies show that both the Cys23 and Ser23 variants can enter the recycling pathway essential for receptor resensitization. Interestingly, receptor distribution within this pathway is altered, with the Ser23 variant having decreased colocalization with the early endosomal maker (EEA1, p<0.05). Thus, the Ser23 variant exhibits a distinct pharmacological and subcellular localization profile vs the Cys23 variant, which could impact aspects of receptor pharmacology like dosing and tolerance to 5-HT2C R ligands in individuals expressing the Cys23Ser SNP.

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In Utero Optical Coherence Tomography to Evaluate Changes in the Murine Fetal Brain Vasculature Due to Prenatal Alcohol and Cannabinoid Exposure

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Abstract

Prenatal substance abuse is one of the main causes of birth defects in the United States. The severity of the defect depends on the substance, amount used, and the period of gestation during which the abuse happened. Many women continue their substance abuse well into the second trimester of their pregnancy, which is considered the peak period for fetal neurogenesis and angiogenesis. Although several studies have documented morphological and behavioral changes due to maternal substance abuse, there is far less research focused on the acute vasculature changes in the fetal brain. In this study we use optical coherence tomography (OCT) to evaluate changes in fetal brain vasculature, in utero, minutes after maternal alcohol and cannabinoid exposure respectively. Ninety-five percent ethanol, diluted in water (water was used for the sham experiments) at a dose of 3g/kg, was administered via intragastric gavage to the pregnant mice after initial (i.e. pre-ethanol) OCT imaging of the embryonic brain. Subsequent measurements were taken every 5 minutes for 45 minutes. CP-55,940, an often-used synthetic cannabinoid in research, was sprayed on the liver of the pregnant mother at a dose of 2 mg/kg after initial OCT measurements. The cannabinoid was suspended in a solution of DMSO: Alkamuls El620 (Rhodia, NJ): lactated Ringer’s (1:1:18), and this solution was used for the sham experiments. Subsequent imaging was performed similar to the alcohol experiments. Results showed a rapid and significant decrease in vessel diameter as compared to the respective sham groups. This preliminary data showed that maternal alcohol or cannabinoid exposure, results in immediate and significant vasoconstriction in the fetal brain.

Figure 1 Fetal brain vasculature (a) before and (b) after maternal alcohol exposure as imaged by SVOCT. (c) Before and (d) after maternal cannabinoid exposure.

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The 5-HT$_2A$ Receptor (5-HT$_2A$R) Regulates Impulsive Action and Cocaine Cue Reactivity in Male Sprague-Dawley Rats

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Impulsivity and the responsivity to cocaine-linked cues (“cue reactivity”) are interlocked contributors to relapse in cocaine use disorder (CUD), and new pharmacotherapeutic strategies that effectively diminish both are likely to promote abstinence in cocaine-dependent individuals. The underlying neurobiology of impulsivity and cue reactivity includes a regulatory role for serotonin (5-HT) neurotransmission, particularly through the 5-HT$_2A$ receptor (5-HT$_2A$R). Systemically administered preferential 5-HT$_2A$R agonists increase while selective 5-HT$_2A$R antagonists/inverse agonists decrease impulsive action, or the inability to withhold a prepotent motor response. Further, selective 5-HT$_2A$R antagonists/inverse agonists consistently reduce both cue- and cocaine-evoked reinstatement of cocaine self-administration (SA) in rodents. The emergence of the clinically-available, FDA-approved 5-HT$_2A$R antagonist/inverse agonist pimavanserin (Nuplazid®) presents a novel pharmacotherapeutic prospect for the management of relapse vulnerability in CUD. We hypothesized that pimavanserin would dose-dependently suppress impulsive action and cocaine cue reactivity during forced abstinence (FA) from cocaine SA in male rats, and we evaluated whether baseline levels of impulsive action would influence the efficacy of pimavanserin to suppress cocaine cue reactivity. The 1-CSRT task was employed to assess premature responses as a measure of impulsive action. A cohort of rats was assessed in the 1-CSRT task prior to acquisition of cocaine SA (0.75 mg/kg/inf). Cue reactivity was assessed as previously-active lever presses reinforced by cocaine-associated cues (e.g., lights, pump sound) at 1 or 30 days of FA from cocaine SA. Pimavanserin (0.3-3 mg/kg) dose-dependently decreased premature responses in the 1-CSRT task ($p<0.05$ vs. vehicle) and previously-active lever presses (1-10 mg/kg) on FA Day 30, but not FA Day 1, from cocaine SA ($p<0.05$ vs. vehicle). A one-way analysis of covariance revealed that baseline levels of impulsive action predicted the efficacy of pimavanserin to suppress cocaine cue reactivity on FA Day 30 ($p<0.05$). The efficacy of pimavanserin to suppress impulsive action and cocaine cue reactivity associated with relapse highlights the therapeutic potential for pimavanserin in the treatment of CUD.

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E-Cigarette Naïve Cigarette Smokers Do Not Exhibit Reductions in Craving After Acute Exposure to E-Cigarettes in the Laboratory

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Background: Recent surveys confirm continued increases in the use of electronic-cigarettes (e-cigarettes). Users often state that e-cigarettes reduce tobacco craving and withdrawal symptoms in addition to their smoking. Prospective laboratory studies and clinical trials indicate that e-cigarettes may decrease cigarette smoking, craving, and withdrawal symptoms, though there are inconsistencies in these outcomes. The objective of this study was to evaluate the effects of e-cigarettes, as compared to the participant’s own cigarette, on craving and choices to smoke.

Methods: Using a within-subjects, placebo-controlled study design, 15 tobacco-dependent (e-cigarette naïve) participants maintained abstinence overnight and then during 4 separate study sessions completed distinct phases of this protocol. Participants were randomized to an e-cigarette device containing one of 3 doses of nicotine (0, 18, or 36 mg/ml) or their own cigarette, with study visits being separated by at least 7 days. Each study session was ~3 hours in duration and included assessments of craving using the 10-item Questionnaire of Smoking Urges (QSU) and Choices to Smoke.

Results: The data show that after 10 puffs breath CO levels increased significantly in the own cigarette condition ($p < .0001$), but not after any e-cigarette dose. QSU scores and choices to smoke were not statistically different across groups after two distinct bouts of 10 puffs each (all $p$’s > 0.1). Additionally, e-cigarette questionnaire responses were not significantly different according to dose (all $p$’s > 0.1).

Conclusions: This experiment provides novel data demonstrating a lack of effects of e-cigarettes on craving or choices to smoke in e-cigarette naïve users.

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Resting Heart Rate Variability Predicts Posttraumatic Stress Disorder Treatment Outcomes in Adults with Co-Occurring Substance Use Disorders and Posttraumatic Stress

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Posttraumatic stress disorder (PTSD) symptoms are highly prevalent among individuals with substance use disorders (SUD), presenting a difficult-to-treat, complex comorbidity. Prognostic factors for treatment outcomes may characterize heterogeneity on the treated population and/or implicate mechanisms of action that are salient for improving treatments. High-frequency heart rate variability (HF-HRV) is a suggested biomarker for emotion regulation: the ability to generate appropriate emotional responses via the influence of the parasympathetic nervous system on the heart. This initial study investigated the utility of HF-HRV for predicting PTSD symptoms and substance use outcomes following treatment of 37 SUD patients with comorbid PTSD symptoms. Participants were randomized to standard cognitive-behavioral therapy (CBT) for SUD or a novel Treatment of Integrated Posttraumatic Stress and Substance use (TIPSS) that combined CBT with cognitive processing for PTSD. Analyses demonstrated an interaction between HF-HRV and treatment condition, indicating greater improvement in PTSD symptoms in the TIPSS, but not the CBT condition. This suggests prognostic value of HF-HRV as a subgroup predictor of PTSD treatment outcomes; those with poorer autonomic emotional regulation may not respond to treatment requiring processing of trauma. This hypothesis-generating analysis identifies a putative biomarker that might have utility in treatment matching.

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Development of Ligands for Serotonin Receptors

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Drug addiction is increasingly viewed as a neuropsychiatric disorder, which places an enormous burden on society. Receptors for serotonin (5-HT) have been implicated in a wide variety of physiological functions both in the CNS and in the periphery. Investigation of 5-HT2AR and 5-HT2CR indicated that they are in oppositional control with 5-HT2AR antagonists and 5-HT2CR agonists exerting similar effects on behaviors such as impulse control and reactivity to cues.1 The combination of subthreshold doses of the 5-HT2AR antagonist M100907 and 5-HT2CR agonist WAY163909 effectively and synergistically suppress impulsivity and cue reactivity in rats was illustrated. To capitalize on this observation, bivalent ligands combining the two compounds by different lengths of a linker were synthesized in our lab.

Our group has reported that M100907 derivatives substituted at the methoxy group of the catechol ring retains its 5-HT2AR antagonist activity. The derivative M100907-azide was synthesized using guaiacol in good yield. Varied positions for the site of the tether on WAY163909 were examined. A position on the phenol ring can retain the agonist activity when it is linked to an ether. The synthesis of the WAY163909-alkyne, starting with 2-amino-4-methoxy benzoic acid, was obtained in few steps including a chiral resolution.

Click reaction was selected allowing for flexible in changing the tether length, high yield, excellent functional group tolerance and the bioorthogonal nature of the azide and alkyne.

In this project, bivalent compounds with M100907 and optically pure WAY163909 have been synthesized. Versions of these ligands attached to cholesterol have also been prepared. In the future, homodimeric derivatives for the WAY163909 will be prepared as well as fluorophore tagged M100907 and WAY163909.

Reference:

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