Role of the Orexin Receptor System at the Nexus of Stress, Sleep and Drug Abuse

Scott Lane, Ph.D.

Stimulant dependence continues to be a significant public health problem, and there are currently no FDA-approved medication options to facilitate abstinence or prevent relapse. Of the stimulants, cocaine presents the largest burden to the healthcare and criminal justice systems in terms of mortality, morbidity, violent crime, and unemployment – and this trend has not declined significantly for decades. Prevalence rates in North America approach 6.5 million users. Cocaine abuse leads to cognitive deficits, compulsive drug use, loss of control over drug-taking, and repeated relapses despite the desire to quit. Even current treatments are marked by high relapse rates, prompting a need for innovative and novel neurobiological research, and eventually new treatment options.

Stress and Anxiety

Complicating the burden of addiction is stress and anxiety, which contribute substantially to all phases in addiction: from risk for binge use, to the onset of dependence, to triggering relapse. Importantly, stress and anxiety increase the magnitude of drug-cue reactivity, and serve as risk factors for both the initiation of substance use and addiction relapse. The use of drugs to reduce physical and psychological stressors has been well documented. Lifetime stress is significantly associated with cocaine use severity.

Sleep

Sleep patterns are disrupted in chronic drug use (including cocaine), including both slow-wave and REM sleep. These disruptions produce deficits in total sleep, and are associated with exacerbation of psychiatric symptoms and declined cognitive function. And there is a reciprocal relationship between cocaine use severity and sleep quality and duration, creating a viscous cycle of impaired sleep, increased stress, and increased risk for cocaine use. Previous studies suggest that medications that improve sleep quality can aid in reducing substance use, and sleep enhancement is a documented treatment
2016 marks the start of several new initiatives at the CNRA.

**On the research front:** The Peter F. McManus Charitable Trust Foundation recently honored Dr. Scott Lane with a grant to investigate the role of stress, sleep dysregulation, and drug craving—critical functions that increase addiction vulnerability. Building upon evidence that the orexin system regulates these functions, the next question Dr. Lane hopes to answer is whether pharmacotherapies targeting the orexinergic system have potential for addiction treatment and relapse prevention.

**On the clinical front:** The INNOVATIONS Clinic at the CNRA recently opened a new behavioral counseling program for addiction treatment. Leading clinician, Dr. Angela Heads, is a licensed Counseling Psychologist with years of experience working with adolescents and adults with substance use disorders and co-occurring behavioral and emotional conditions. She joins Dr. Michael Weaver, addiction medicine physician for INNOVATIONS, in offering patients a clinically effective combination of behavioral counseling with medication-assisted treatment for addiction. For more information or to schedule an appointment, please call (713) 486-2700 (INNOVATIONS is part of the UT Physicians Psychiatry Outpatient clinic practice of the John P. and Kathrine G. McGovern Medical School.)

**On the dissemination and outreach fronts:** Find CNRA on Facebook! Our goal is to use social media as another way to reach the community with the latest news and information from the CNRA and from research centers nationwide. Make sure to visit and “like” us at [www.facebook.com/UTHealthCNRA](http://www.facebook.com/UTHealthCNRA)!

**Upcoming Events**

**UTHealth Stomp Out Stroke Festival**  
Saturday April 30th 2016  
Water-Works Buffalo Bayou Park

- Free, open to the public, family-friendly event
- Stroke and brain health education
- Free health screenings
- Entertainment, performances, & music

Visit the CNRA at the Brain on Drugs booth in the Kid’s Zone.  

*Register at [www.strokefestival.org](http://www.strokefestival.org)*
strategy for substance use disorders.

**Drug Cues**

Reactivity to drug cues is a robust predictor of relapse. This relationship has been established for a variety of abused drugs, including cocaine. Craving and biased attention toward drug-related stimuli (i.e., settings, drug paraphernalia) are two of the best-documented indices of reactivity to drug cues, and have been identified as factors in nearly every major drug of abuse.

These factors are predictive of relapse following treatment, and are now considered hallmark characteristics of addiction. Importantly, both craving and biased attention toward drug cues bias can be reduced through medications.

**Novelty and promise of the orexin system**

The orexins are a class of recently discovered peptides that are widely distributed throughout the brain. The orexin system is neuromodulatory, meaning that it activates a number of brain circuits through the regulation of two major neurotransmitters: glutamate and GABA.

The primary role of the orexin system appears to be in balancing the brain’s energy needs (e.g., arousal and awareness). Accordingly, blocking the action of the orexin system (a process called antagonism) promotes sleep.

Importantly, research suggests that orexin antagonists modify three key cocaine-related variables described above: stress/anxiety, sleep, and drug-cue reactivity. Suvorexant is currently the only FDA approved compound that acts on the orexin receptor system. It is indicated for treatment of insomnia.

In the present study, funded by an award from the Peter McManus Charitable Trust to Dr. Scott Lane, CNRA researchers will investigate the effect of suvorexant to regulate the interactions among drug-cue reactivity, anxiety/stress, and sleep in individuals with cocaine abuse – hypothesizing that suvorexant may be an effective medication for the prevention of relapse in cocaine abuse.

The CNRA research team will use laboratory measures of risk for relapse, including measurement of eye-movements in the presence of drug-related cues, developed by Dr. Lane (described in CNRA Newsletter, January 2014). Additionally, Dr. Jin Yoon will coordinate state of the art wearable activity/sleep monitors and text-messaging services to be utilized in data collection and adherence to taking the medication daily over several weeks.

This study will represent the first examination of the orexin system in humans struggling with substance abuse. CNRA researchers hope to show medications that modulate the orexin system may be effective in the quest to treat those with substance use disorders, especially in the prevention of relapse.

The CNRA will begin to recruit research volunteers with cocaine dependence in the Spring of 2016.
It starts with the right ingredients – an intriguing scientific premise, a compelling research question, a testable hypothesis, pilot funds, and enthusiastic researchers. Two years and thirty enrolled participants later, the results are organized and critically assessed with the possible outcomes. Positive findings → race to present, publish, and apply for more funding. Negative findings → identify study limitations, file under “failed studies,” and move on with a stiff upper lip.

Increasingly in recent years, this “recipe” for scientific discovery has come under close scrutiny and calls for reformulation. “Enhancing reproducibility through rigor and transparency” is the new buzz-phrase at the National Institutes of Health (NIH). It is time to improve the recipe by adding a generous dose of checks and balances to ensure best practices in scientific research.

**Check 1: Is there a strong scientific premise for the research?**

Even the newest avant-garde entrees from high-end restaurants are based on previous successes and failures. Likewise, all research builds upon prior research: The stronger the base, the sturdier the foundation or premise for new research. Sometimes the enthusiastic researcher, armed with positive findings from a pilot study, forges ahead with the next study without carefully addressing the strengths and weaknesses of existing data. The discouraged researcher may shove negative findings into the proverbial file drawer, out of side and out of mind, without considering that research done properly will produce negative results – as much as half of the time! Reporting negative results, especially when they point out scientific flaws in previously published work, is an important step toward enhancing reproducibility. Bottom line: A good scientist must evaluate the premise for their research by identifying strengths and weaknesses of prior work in order to propose ways to improve going forward.

**Check 2: Is the research consistent with rigorous experimental design?**

A good recipe carefully describes the ingredients and techniques required to make a dish. In science, this means including critical methodological details and procedures – step-by-step – so that even a novice can follow the well-written recipe to obtain the same results. The message here is to document and report every aspect of your work. Start with participants. What eligibility criteria were used for selection? How were participants assigned to experimental conditions? How was the size of the study sample determined? How many participants completed the study? How many dropped out and why? End with results. What statistical analyses were undertaken? How precise (or uncertain) are the estimated effect sizes of the intervention? Do any study results generalize to other individuals with different characteristics in regard to age, sex, gender? Full transparency in reporting study details will allow other researchers to reproduce and extend the findings.

**Check 3: Is the trial registered?**

Think of national registries such as ClinicalTrials.gov as the public “menu” for researchers. Enter your protocol (recipe) with standard reporting elements _continued on page 5_
Ensuring Best Practices, continued from page 4

(ingredients), and then submit timely updates and summary results. Everyone benefits. Patients and clinicians can search for a new treatment study for a specific disease. Journal editors and granting agencies can find detailed information about the trial design, procedures, and results. The general public can learn how research results contribute to medical knowledge.

Check out the CNRA trials posted on ClinicalTrials.gov!

- NCT00439049 Substance Abuse Pre-Treatment Screening Study
- NCT01535573 Citalopram for Cocaine Dependence
- NCT01393457 Cognitive Remediation for Cocaine Dependence
- NCT02461732 Trial of a Novel Cognitive-Behavioral Treatment for Posttraumatic Stress and Substance Dependence

New Faces at the CNRA

**Jafar Bakhshaie, M.D.** is a practicum student, currently working on the Trial of Novel Treatment of Posttraumatic Stress and Substance Dependence study. He is a third-year doctoral student in the clinical psychology program at the University of Houston. Dr. Bakhshaie’s research focuses on exploring emotional regulatory mechanisms and cognitive processes underlying substance use disorders and panic/PTSD comorbidities. He research interests include emotional regulatory and reactivity processes as underlying processes of substance use-anxiety/stress comorbidity with important clinical implications.

**Melissa Fasteau, M.A.,** is a pre-doctoral intern from Yeshiva University/Ferkauf Graduate School of Psychology. She has trained in a variety of clinical settings, including college counseling centers, outpatient community and hospital clinics, and an inpatient psychiatric hospital. Her training focuses on evidence-based interventions, including CBT for anxiety, depression, and addictions, Motivational Interviewing, and Exposure and Ritual Prevention. She is completing a 6 month rotation at the CNRA. Her dissertation research focuses on the intersection of low-income adolescents’ perceptions of political fairness, dispositional optimism, and goal-setting behavior.

**Ilana Haliwa, B.A.,** is a Research Assistant working with Dr. Jin Yoon on the Assessment of Cigarette Smoking among Candidates for Cardiovascular Surgery and Perioperative Outcome study, the Nicotine and Tobacco Use in Cardiac Patients study, as well as the Abuse Liability of E-cigarettes following Administration of Alcohol and Exposure to Alcohol Cues among College Students study. She earned her B.A. in Psychology from the University of North Carolina at Chapel Hill and is currently in the process of completing her Master's in Public Health through Nova Southeastern University.

**Nausheen Noor, M.A., M.Ed.,** is a doctoral student in Counseling Psychology at University of Houston. Her research focuses on cultural factors that influence the adjustment of immigrants in the U.S. She has worked with trauma and substance use disorders in various settings. She is doing her doctoral practicum at the CNRA as a therapist working on the Trial of Novel Treatment of Posttraumatic Stress and Substance Dependence study and Clinical Trial of Citalopram in Cocaine Dependence studies.

**Jonika Tannous** is a first year neuroscience PhD student at GSBS. She has a background in cognitive science, psychology, and neuroimaging. She intends to investigate Diffusion-Weighted Tensor Imaging (DTI) as a diagnostic tool in psychiatry throughout her graduate career. She is currently rotating in Dr. Scott Lane’s lab and is studying white matter abnormalities in patients with cocaine and alcohol disorders.
2016 Selected Faculty Publications


- Alcorn III, JL, Rathnayaka N, Swann AC, Moeller FG, **Lane SD**: Effects of intranasal oxytocin on aggressive responding in Antisocial Personality Disorder. The Psychological Record, in press.


- Bershad AK, Weafer JJ, Kirkpatrick MG, Wardle MC, Miller MA, de Wit H: Oxytocin receptor gene variation predicts subjective responses to MDMA. Social Neuroscience, in press.


- Dias NR, **Schmitz JM**, Rathnayaka N, Red SD, Sereno AB, Moeller FG, **Lane SD**: Anti-saccade error rates as a measure of attentional bias in cocaine dependent subjects. Behavioural Brain Research, 292, 493-499, 2015.


- Wardle MC, Bershad AK, & de Wit H: Naltrexone alters the processing of social and emotional stimuli in healthy adults. *Social Neuroscience*, in press.


CNRA is pleased to announce that the INNOVATIONS Clinic is offering behavioral therapy services to complement the Medication-Assisted Treatment (MAT) program for substance use disorders. Dr. Angela Heads, a licensed psychologist, is accepting new patients who are interested in receiving individual therapy to help in their recovery from drug addiction, including tobacco, alcohol, prescription medications, and other illegal substances.

“Working with Dr. Weaver (MAT director), I believe the combination of medication with behavioral therapy is the right formula for success. I’m proud to be part of a program that adheres to current best practice guidelines as defined by national and international health organizations, such as the American Society of Addiction Medicine (ASAM), the Substance Abuse and Mental Health Services Administration (SAMHSA) and the World Health Organization.”

Dr. Heads has over 15 years of experience as a psychotherapist. She is also a clinician-scientist with research publications and presentations on topics related to health disparities, gender, trauma, and addiction. Her goal as a therapist is to assist each individual in setting value-based goals and taking actions toward changing how they think and behave.

Drs. Weaver and Heads work as a team in evaluating and developing a personalized and comprehensive treatment plan that involves medication management and ongoing psychotherapy.

“Psychotherapy is sometimes referred to as ‘talk therapy,’” Heads explains. “Research has shown that psychotherapy is an essential part of substance use treatment for many people. Specifically, the use of interventions such as cognitive behavioral therapies, motivational interviewing and mindfulness-based interventions have been shown to be effective in helping people to recover from addiction.”

For individuals who achieve abstinence, psychotherapy has been shown to reduce the risk of relapse by providing strategies for managing stress, dealing with cravings, and developing healthy coping strategies. Psychotherapy can also help people stay in treatment longer, thereby allowing them to experience the full effectiveness of their medications.

Psychiatric comorbidity (the co-occurrence of a mental health condition) is known to complicate treatment for individuals with substance use disorders. Research has shown a tendency for poorer outcomes including higher relapse rates among substance users who also have a comorbid psychiatric condition such as depression or posttraumatic stress disorder. The first-line treatment approach for all comorbid disorders is integrated psychotherapy that targets comorbid conditions concurrently. The most promising integrated treatments for patients with comorbid conditions are offered at the INNOVATIONS clinic.

The INNOVATIONS Clinic participates with multiple health insurance plans, including Medicare and Medicaid. Appointments are currently available with minimal wait time. The INNOVATIONS Clinic is located on the campus of the Texas Medical Center close to the CNRA, with ample surface parking nearby. For additional information, to refer a patient, or to schedule an appointment, please call the UT Psychiatry Clinic. 713-486-2525
Recent Awards, Recognition, Honors

◊ **Dr. Scott Lane** was awarded the Peter F. McManus Charitable Trust Foundation Grant for his study entitled, “Role of the orexin receptor system at the nexus of stress, sleep and drug abuse.”

◊ **Dr. Anka Vujanovic** was invited to present “PTSD and Substance Use Disorders: A Clinical Overview” at the Seventh Annual UTHealth Psychiatry Update in Houston, Texas, February 2016.

◊ **Dr. Angela Heads** joined the CNRA faculty as Lead Therapist of the behavioral treatment program at INNOVATIONS Clinic.

◊ **Dr. Michael Weaver** was invited to present “Alcohol Use Disorder and Chronic Pain,” at the PAINWeek 2015 National Conference, Las Vegas, NV, September 2015.

◊ **Dr. Michael Weaver** was invited as a Panelist to present “Medication-Assisted Treatment” at the Texas Association of Addiction Professionals, Houston TX, October 2015.

◊ **Jocelyn Abrams**, a visiting research assistant at the CNRA and pre-doctoral counseling trainee at the University of Houston was accepted into Yale School of Medicine Clinical Psychology Internship program.

◊ **Dr. Vujanovic**, in collaboration with Drs. Bonn-Miller and Petry, was invited to serve as Guest Editor of a special section on co-occurring posttraumatic stress and substance use disorders for an upcoming issue of Psychology of Addictive Behaviors.

◊ **Dr. Schmitz**, in collaboration with Drs. Copeland and Cropsey, was invited to serve as Guest Editor of a special issue on special populations and comorbidity issues in nicotine dependence for the Journal of Addiction.

Your Support Is Needed

Contributions to CNRA help advance important research to develop science-based treatments for those who suffer from substance use disorders.

Donations can be made to:

Office of Development
Attn: B. Henry/CNRA
P.O. Box 1321Houston, TX 77251-1321

Funds provided by the Faillace Endowed Professorship, established in 2011 by **Cynthia and Ray Wright** in honor of **Louis A. Faillace, M.D.**, supports excellence in psychiatric research and patient care, and envelopes the mission of the CRNA – to develop evidence-based addiction treatment.
Inside the CNRA

The CNRA currently has three ongoing studies of treatment for substance use disorders.

- Clinical Trial of Citalopram in Cocaine Dependence
- Cognitive-enhancing Dopamine Medications for Cocaine Dependence
- Treatment of Integrated Posttraumatic Stress and Substance Use

CNRA Program Features:

- No Cost Treatment
- 100% confidential
- Medical & Behavioral Treatments
- Experienced and Professional Staff
- A Safe and Clean Atmosphere
- Free Parking and Metro Tickets
- Financial Compensation for Research Participation
- Funded by the National Institute on Drug Abuse (NIDA)

Appointments:

713-500-DRUG (3784)

Clinic Hours:
Monday – Friday 7:30-4:00

Behavioral and Biomedical Sciences Building
1941 East Road
Houston Texas 77054

https://med.uth.edu/psychiatry/research/addiction/