Center Line

Bowles Center for Alcohol Studies
School of Medicine, University of North Carolina at Chapel Hill

Our mission is to conduct, coordinate, and promote basic and clinical research on the causes, prevention, and treatment of alcoholism and alcoholic disease.

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Breaking the Habit: Scientist's Research Will Reveal Mechanisms of and Potential Targets for Maladaptive Alcohol Drinking

Alcoholics often describe their initial experiences with alcohol in very positive terms. Drinking made them feel happy, expansive, even euphoric; it increased their self-confidence and sense of well-being. It is not difficult to understand why someone experiencing these effects of alcohol might continue to seek it out.

While the rewarding effects of alcohol appear to support continued drinking early in the course of alcoholism, they appear to dissipate over time with repeated use of alcohol and are rarely described as reasons for drinking by those with advanced alcoholism. In contrast to the occasional drinker who imbibes in order to experience positive effects, many alcoholics continue to drink even when they experience little positive reinforcement from it. In fact, many alcoholics continue to drink despite experiencing significant negative effects of alcohol. These points are illustrated by the character of Henry Chinaski, the fictional alter ego of his creator Charles Bukowski, the famously alcoholic author known as the "Poet Laureate of Skid Row." After a night of drinking (writes essayist Adam Cohen in *Visions of Bukowski*), Chinaski often "awoke in cheaply rented bedrooms, probably hostels (if he was lucky enough to afford them). Typically, he stumbled out of bed, towards the toilet, and got sick, his binging now turning into purging. Walking back into the bedroom, he'd sit down at his desk and pull another bottle of beer from a mini-fridge at his feet. While sucking back and gasping at the bottle, his female counterpart asks "How do you feel?", to which he replies, "I feel bad. I wanna be alone." (from www.litkicks.com/VisionsOfBukowski)

Robinson Lab (left to right): Kate Smith, Ph.D., Lihan Deng, Dawnya Bohager, M.S., Donita Robinson, Ph.D., Josh Jennings, Becca Reese, Randall Ung, Rachel Hay, Vahid Sanii, Sebastian Cerdena.

The motivation for such drinking seems much more difficult to understand than the positive effects that appear to motivate occasional drinking or drinking in the early stages of alcoholism. Neither motivated by positive outcomes nor mitigated by negative outcomes such as illness, Chinaski's drinking seems to be disconnected from its consequences. Behavioral scientists characterize such behaviors as *habits*: actions that are driven by conditioned cues and that are independent of outcome. In her memoir *Note Found in a Bottle: My Life as a Drinker*, Susan Cheever aptly describes the habitual nature of alcoholic drinking: "These were years when I was drinking, but I don't even remember the drinking. I was acting as if I were a marionette being pulled around by . . . invisible strings . . ." Such habitual drinking differs from what behavioral scientists characterize as *goal-directed behavior*—that is, actions that are dependent on outcomes—drinking motivated by the reward of feeling good, for example.

Dr. Donita Robinson, Assistant Professor in the Department of Psychiatry and the Bowles Center for Alcohol Studies at UNC, believes that understanding the behavioral and physiological underpinnings of habitual drinking could hold keys to curbing the development of alcohol dependence and to preventing relapse. Robinson models both goal-directed alcohol drinking and habitual alcohol drinking in rats trained to press a lever to receive alcohol. To elicit goal-directed alcohol drinking, Robinson uses a *fixed-ratio 5 reinforcement schedule* in which every five lever presses yields a drink of alcohol. Drinking behavior established on this

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Donita Robinson, Ph.D.

Affiliations

Assistant Professor, Department of Psychiatry and Bowles Center for Alcohol Studies, UNC School of Medicine; Director, Behavioral and Pharmacological Neurodynamics Lab

Education and Training

Postdoctoral Fellowship in Analytical Chemistry, University of North Carolina at Chapel Hill, 2002; Ph.D., Neuroscience, University of Texas at Austin, 2000; M.A., Biological Psychology, University of Michigan at Ann Arbor, 1993; B.A., Psychology, University of Texas at Austin, 1991.

Publications

D.L. Robinson, E.C. Howard, S. McConnell, R.A. Gonzales, R.M. Wightman (2009). Disparity between tonic and phasic ethanol-induced dopamine increases in the nucleus accumbens of rats. Alcoholism: Clinical and Experimental Research, 33: 1-10.

D.L. Robinson, R.M. Carelli (2008). Distinct subsets of nucleus accumbens neurons encode operant responding for ethanol versus water. European Journal of Neuroscience, 28:1887-1894.

D.L. Robinson, A. Hermans, A.T. Seipel and R.M. Wightman (2008). Monitoring rapid chemical communication in the brain. Chemical Reviews, 108: 2554-2584.

Website

www.med.unc.edu/alcohol/robinson

schedule is easily extinguished such that when a rat is no longer given the alcohol after five lever presses, the rat soon ceases to press the lever. Under this reinforcement schedule, the rat unable to achieve the "goal" of the drink of alcohol no longer performs the goal-directed behavior of lever pressing. To elicit habitual alcohol drinking, Robinson uses a *variable-interval 30-second reinforcement schedule* in which a variable amount of time (on average 30 seconds) must go by before a lever press will earn a drink of alcohol. The variable-interval 30-second reinforcement schedule produces behavior that mimics the habitual drinking of the human alcoholic in that it is resistant to extinction and not influenced by reward devaluation. Resistance to extinction is demonstrated by the finding that, even when lever presses no longer yield alcohol, the rat continues to press the lever. Reward devaluation is demonstrated by the finding that, even when the alcohol is made less rewarding by pre-exposing the animal to as much alcohol as it cares to drink before the lever-pressing task, the rat continues to press the lever to seek alcohol. The resistance to extinction and to the effects of reward devaluation resembles the behavior of the alcoholic who continues to drink even when drinking no longer elicits good feelings.

What changes in the brain mediate the transition from goal-directed drinking to habitual drinking in the alcoholic? Robinson was recently awarded a five-year grant from the National Institute of Alcohol Abuse and Alcoholism to address this question by using two state-of-the-art techniques to study the activity of nerve cells (neurons) in rats trained to press a lever to receive alcohol. First, Robinson uses the technique of extracellular recording at multielectrode arrays to characterize the electrical activity of small groups of neurons. Second, Robinson uses the technique of fast-scan cyclic voltammetry to gauge release of dopamine, a neurochemical that (among others) is important in mediating the functioning of the brain's reward circuit. These measurements are made in real time while the animal is seeking and drinking alcohol. Robinson is focusing her efforts on the dorsomedial striatum and the dorsolateral striatum—areas that form part of the brain's reward circuit and that have been implicated in goal-directed and habitual behavior. Previous data in animals suggest that the dorsomedial striatum is involved in goal-directed drug-taking behavior whereas the dorsolateral striatum is involved in habitual drug-taking behavior. These data and other results are consistent with the possibility that the transition from goal-directed alcohol drinking to habitual alcohol drinking is associated with an anatomical shift of information processing from the dorsomedial striatum to the dorsolateral striatum. Robinson will explore this possibility by comparing brain activity in rats trained on the fixed-ratio 5 reinforcement schedule (to produce goal-directed drinking) with that in rats trained on the variable-interval 30-second reinforcement schedule (to produce habitual drinking). She hypothesizes that the neurons in the dorsomedial striatum will be preferentially active during goal-directed alcohol reinforcement whereas neurons in the dorsolateral striatum will be preferentially active during habitual alcohol reinforcement. Neural activity and dopamine release in these two brain areas will be assessed during alcohol self-administration; during extinction, in which alcohol delivery

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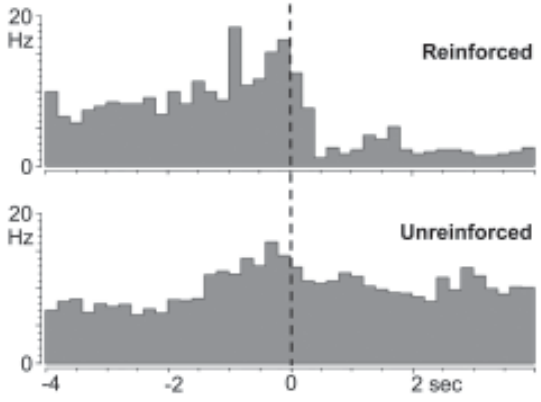

Figure: Representative phasic firing of a neuron in the dorsolateral striatum, a brain region involved in habitual behaviors. Neuronal firing before and after lever presses that are reinforced with an alcohol reward (top graph) or are not reinforced (bottom graph). This neuron increases firing rate leading up to the lever press, then dramatically decreases firing at reinforcement, but not when a press was unreinforced. The firing patterns of neurons in the dorsal striatum are thought to reflect the integration of cortical and subcortical inputs that in turn direct the rat's operant behavior.

The Director's Column

Fulton T. Crews, Ph.D.
Director,
Bowles Center for Alcohol Studies

As time moves, things change. At the Center, we are growing new young faculty like Donita Robinson, but unfortunately our senior accomplished faculty sometimes decide it is time to play with their grandchildren, as David Overstreet decided. For many years, Overstreet investigated drug effects on rodent alcohol drinking and contributed to the discovery that opiate antagonists reduce alcohol drinking. Naltrexone, an opiate antagonist, is now clinically used to help alcoholics maintain abstinence. David will spend his retirement with his wife and children in Hawaii, Arizona and Australia.

Donita Robinson is pushing the cutting edge of our understanding of brain function in new and extraordinary directions. Her work indicates that the transition from drug experimentation to excessive-compulsive drug taking is related to changes in behavior and brain signaling that involve specific sites in brain that are not activated during experimentation with drugs, but only become active and important during habitual drug taking. These discoveries are helping better define the neurobiology of addiction.

The knowledge generated by Overstreet and his contemporaries is being used by Robinson to investigate potential drugs that could block the compulsive habitual drives of addiction. These new and novel neurobiological processes are likely to help find new and better pharmacotherapies for alcoholism. I believe young scientists like Donita Robinson will carry the science further and the next generation will make discoveries that give us robust effective medications that help people break their compulsive drug habits. Change can be painful but is needed to advance science and medicine. Thus, all senior faculty at the Center will continue to mentor new faculty to carry the cause forward. ■

Carolinas Conference on Addiction and Recovery

The Carolina's Conference on Addiction and Recovery was held in Chapel Hill from Oct. 27-30, 2009. This year's theme, "Creating Recovery Oriented Communities of Care," focused on bringing primary medical care professionals closer together with the substance abuse counseling community with an emphasis on screening and brief interventions. Dr. Fulton Crews, UNC, opened the conference of 24 presentations to 150 attendees from 12 states. Nineteen exhibitors represented treatment programs, material suppliers, technology suppliers, pharmaceutical representatives and recovery support services. The Bowles Center for Alcohol Studies with the Addiction Recovery Institute received added support from the NC Governor's Institute and the Medical University of South Carolina Alcohol Research Center. During the multi-day conference, topics included best practices, co-morbidity, family therapy, treatment of veterans and tools for successful recovery. A major emphasis was Screening, Brief Intervention and Referrals to Treatment (SBIRT). Dr. Howard Moss, NIAAA, reviewed his studies indicating five subtypes of alcohol dependence that includes large groups of individuals who never receive counseling. Dr. Thomas Babor, University of Connecticut, covered the value of SBIRT in reducing drinking and health risks. Ms. Joan Peters, Physician Financial Solutions, presented how to include SBIRT in medical practice and cover the cost of screening. The Carolina Conference on Addiction and Recovery continues to bring scientific discovery and science based practices to the treatment community. ■

CONGRATULATIONS
to
Dr. John J. Lemasters
on Receiving the
2009 Thurman Lectureship Award

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is ceased in animals previously trained to press the lever for alcohol; and during reinstatement, in which alcohol delivery is reinitiated in animals that had previously undergone extinction.

"Our work should provide the most complete picture to date of how the brain encodes alcohol-related habit formation," says Robinson. "The disconnection of the drinking behavior from its consequences is a major factor that makes alcoholism so difficult to treat. Alcoholics continue to drink despite negative consequences and devaluation of alcohol by tolerance. If we can understand how the brain wires itself or changes its coding to support this maladaptive behavior, we can begin to investigate therapeutic approaches that can control habitual drinking."

In fact, Robinson was recently awarded a supplemental two-year grant to study the effects of drugs in her model. Animal models previously used to screen drugs for potential usefulness in human alcoholics have almost exclusively employed goal-directed reinforcement schedules. Robinson will study drugs under both goal-directed reinforcement schedules and habitual reinforcement schedules. She hypothesizes that naltrexone, a drug that appears to make alcohol less rewarding, will be less effective in reducing alcohol drinking under habitual reinforcement schedules (i.e., variable-interval schedules) than under goal-directed reinforcement schedules (i.e., fixed-ratio). Further, she hypothesizes that topiramate, a drug that stabilizes neurocircuitry, will be effective in reducing alcohol drinking under the habitual reinforcement schedule. By opening the door to studying drug effects in habitual drinking, these experiments could lead to improved preclinical animal models of alcohol drinking and relapse-like behavior. ■

UNC Bowles Center for Alcohol Studies
CB# 7178, Thurston-Bowles Building
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina 27599-7178

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CAS Bids Farewell to Long-Time Researcher Overstreet

With 40 years of research and nearly 300 publications under his belt, David H. Overstreet, Ph.D., gave a farewell seminar to family, friends and colleagues in September on the UNC Campus. The seminar marked Overstreet's retirement after a long and remarkable career in research. He plans to spend most of his newly found free time with family in Arizona and California.

Overstreet's seminar, "Can 2-Bottle Choice Still Be Used Effectively to Study Alcohol Drinking," highlighted his own work with colleagues across a successful history of basic strategies to measure ethanol preference in animal models. After his seminar, Overstreet was presented with a plaque in recognition of a lifetime of research discoveries.

Judy and David Overstreet with Fulton Crews

In his 20 years at the UNC Bowles Center for Alcohol Studies, Overstreet published nearly 10 manuscripts per year with a primary emphasis on animal models of alcoholism and depression. Overstreet was a key player in the development of the Flinders Sensitive rat line (FSL, a model of depression) and the Fawn Hooded rat line (FH/Wjd, a model of comorbid depression and alcoholism), both of which have been extensively used in the study of the behavioral and neurobiological mechanisms of these human conditions. He has published widely on models of anxiety and ethanol withdrawal, novel compounds, cholinergic function, and more.

Overstreet will continue to collaborate with close colleagues George Breese, Ph.D., and Darin Knapp, Ph.D. on corticotrophin releasing factor (CRF) as well as other mediators of anxiety after alcohol withdrawal. He is also finalizing collaborations with other UNC faculty members on the effects of pregnenolone and oxytocin on alcohol drinking.

Overstreet graduated Phi Beta Kappa with a B.A. in psychology from the University of California, Berkeley. In 1972, he received a Ph.D. in psychobiology from the University of California, Irvine. Overstreet joined the Bowles Center and the Department of Psychiatry in 1990.

"David Overstreet's retirement will produce a 'vacuum' for the laboratory. While we will miss his quick wit, we will miss more the major contributions he has made to the successes our laboratory has enjoyed," said Breese. ■

The Bowles Center for Alcohol Studies

Tel. (919) 966-5678
Fax. (919) 966-5679

To become involved in our mission, call Elizabeth Thomas at (919) 966-4977 or email ethomas@med.unc.edu.

For treatment information call UNC Health Care's Alcohol and Substance Abuse Program at (919) 966-6039 or (888) 457-7457.

www.med.unc.edu/alcohol

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A. Leslie Morrow, Ph.D., Editor-in-Chief; Elizabeth Thomas, Managing Editor; Jane Saiers, Ph.D., Science Writer

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