Behavioral and cognitive processes underlying substance use disorders

By Scott D. Lane, Ph.D.

Abstract: Individuals with substance use disorders have prominent, measurable patterns of maladaptive behavior and cognition, most notably impulse control problems, inflexibility in information (stimulus-reward) processing, and decision-making biases toward high-risk/high-reward alternatives. Therapeutic interventions (including medications) that target remediation of cognitive-behavioral deficits may be important tools in the treatment of substance use disorders.

Substance use disorders (SUDs) are marked by a constellation of behavior patterns that contribute to three key stages: the initiation of drug use, escalation to binge use (abuse), and the maintenance of chronic, compulsive use patterns (dependence). This constellation includes diminished inhibitory control (impulsivity); inflexibility in learning (adapting to demands of changing contexts and contingencies); risky decision-making marked by high reward (and potentially highly aversive) options; and – further down the pathway from abuse to addiction – affective instability and an inappropriate attentional bias to drug-related cues (e.g., sensory stimuli that have become associated with drug use). A conceptual rendering of this premise is provided in the accompanying figure (Figure 1). Longitudinal data from twin and catchment-area studies reveal that these behavior patterns are present in childhood or

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Cognitive remediation approaches to improve drug abuse treatment outcomes

By Joy M. Schmitz, Ph.D.

Abstract: A significant proportion of patients with substance use disorders, including cocaine dependence, have measurable cognitive impairment, and the presence of these impairments negatively affects treatment outcome. Recent supporting evidence suggests that improving cognition may be the most direct path to improving drug use treatment outcome.

Over the last few decades, cocaine addiction has attained epidemic proportions in North America, imposing a tremendous burden on society and the health care system. An estimated 25 to 33 million Americans report experimenting with cocaine; five to six million of these on a regular basis. Repeated cocaine use can produce addiction and other adverse health consequences. In addition, chronic use of cocaine is associated with structural and metabolic abnormalities in the brain, particularly in regions considered important for executive control. It follows that adults diagnosed with cocaine dependence have been found to have measurable deficits on cognitive tasks involving attention, planning, decision-making, and self-regulating behavior. Several

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This issue of the NRC Newsletter marks the mid point in our programs for the academic year. We are off to a great start and the next six months look equally exciting.

The Annual NRC Poster Session was held on December 4, 2010. Now in its 17th year, the Poster Session is designed to promote the scientific exchange of information among our students, postdoctoral fellows and faculty. Too frequently, we limit our interactions to those in a nearby corridor or building. The poster session allows NRC members to interact informally and learn about new scientific developments. We had a wonderful turn out and continued our tradition of awarding prizes to the outstanding presenters. Bryan Hansen (Valentin Dragoi Lab) was the recipient of the first-place prize, the “Dee S. and Patricia Osborne Endowed Scholarship in the Neurosciences”, in the graduate student category. The second-place prize was awarded to Anu Rambhadran (Vasanthi Jayaraman Lab), and third place to Michelle Reith (Michael Gambello Lab). In the postdoctoral category, Nader Ezzeddine (Eric Wagner Lab) and Yan-Gang Sun (Michael Beierlein Lab) shared the first place prize and third place was awarded to Yiyan Zheng (Qilin Cao Lab). The NRC is greatful for the many judges from UT, Rice and Baylor who devoted their time and expertise.

This year we continued the competition for the NRC “Distinguished Medical Student in the Neurosciences Award”. Candidates for this award are fourth year M.D. or M.D./Ph.D. students who have demonstrated excellence in research in the neurosciences and plan to follow a medical career in neurology, neuroimaging, neurosurgery, or other neuro-related field. This year the recipient was Saint Aaron Morris, who had worked with NRC faculty members in the Department of Neurosurgery. He will receive his award at the NRC Annual Public Forum on February 12, 2011.

This marks the 11th year that the NRC has hosted a course focusing on the Neurobiology of Disease. The first course at The University of Texas Medical School at Houston (UTHealth) was organized by James Ferrendelli, who had recently arrived at UTHealth from Washington University. Since the beginning, we have placed intensive focus on a single area, rather than attempting to cover all brain disorders. This year’s topic was “Genetic Basis for Brain Diseases”, and the course was directed by Teresa Santiago-Sim, NRC member from the Department of Neurosurgery. The course was an integrated approach to understanding inherited brain diseases, with lecturers from faculty at UTHealth, M.D. Anderson Cancer Center, and Baylor College of Medicine. In addition, we supplemented the local talent with a lecture by Anthony LaMania of the George Washington University School of Medicine.

The NRC will host our 16th Annual Public Forum February 12, 2011 on “Bipolar Disorder and Depression” in conjunction with Brain Awareness Week. The public forum will consist of a panel of experts from UTHealth. The moderator will be Jair Soares, Chairman of the Department of Psychiatry and Behavioral Sciences and the panel will include Oscar Bukstein, Pranshant Gajwani, Associate Professor and Vice Chair of Clinical Affairs and Alan Swann, Professor and Vice Chair of Research of the Department of Psychiatry and Behavioral Sciences.

Another major event associated with Brain Awareness Week is Brain Night, which will be held at the John P. McGovern Museum of Health and Medical Science. This event is part of our Partners in Education (PIE) program for the Neurosciences in Houston, and involves the coordination of various ‘Partners’, including the Museum, area elementary schools, UT Physicians, and an enthusiastic volunteer base of NRC faculty members, postdoctoral fellows, and graduate students from UTHealth. Brain Night will be attended by elementary school age children and their families, and will be packed with activities from mini-lectures on the human brain, MRIs, brain attacks (stroke) demonstrations on helmet safety, brain reflexes, eye-hand coordination, and comparative brains of species. Students will have the chance to handle an actual human brain, an increasingly popular demonstration. Brain Night is scheduled during Spring Break, March 17, 2011.

Our most notable venue of the year is our NRC Distinguished Lecture. Since 1992, we have hosted lectures given by eminent scientists of national and international repute who are Nobel Laureates or who could be future Nobel Laureates. This year’s Distinguished Lecture will be given by Daniel Weinberger, Senior Investigator of the Clinical Brain Disorders Branch at NIMH. He will present his talk on May 12, 2011.

The mission of the NRC is to facilitate scientific research and collaborative efforts in the neurosciences, to disseminate information about brain-related discoveries to the scientific and educated public, and to foster knowledge about the brain and neuroscience opportunities to the general public, schools and interest groups as part of a community outreach program. We have been very successful in fulfilling this mission and will enthusiastically continue our efforts.
**Grants & Awards**

**Claudio Soto,** Department of Neurology, UTHealth, has been awarded a three-year, $200,000 grant by The Alzheimer’s Association to pursue a procedure that could detect pre-symptomatic Alzheimer’s disease.

**Valentin Dragoi,** Department Neurobiology and Anatomy, UTHealth, is one of 17 researchers to win a 2010 National Institutes of Health Director’s Pioneer Award. The award will provide funding for Dr Dragoi’s groundbreaking proposal to examine population coding underlying complex behavior in freely moving primates. The NIH Director’s Pioneer Awards are designed to support individual scientists of exceptional creativity who propose pioneering – and possibly transforming approaches – to major challenges in biomedical and behavioral research.

**Anthony Wright,** Department of Neurology, UTHealth, has been elected as a fellow of the Society of Experimental Psychologists (SEP). The Society of Experimentalists was founded by Edward Bradford Titchener in 1904. Titchener’s design for his “Experimentalists” was that it be an ongoing workshop, with “members visiting labs, studying apparatus, and hearing and commenting on reports of ongoing research.”

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**NRC 2010 Poster Session Winners**

L to R: Michelle Reith, Anu Rambhadran and Nader Ezzeddine

Bryan Hansen and Valentin Dragoi

Yan-Gang Sun and Michael Beierlein

Yiyan Zheng
early adolescence, manifested in poor school performance, oppositional behavior, conduct problems, risk/sensation seeking, and early experimentation with drugs – particularly nicotine, alcohol and marijuana. The risk for both substance abuse and the above-noted behavioral problems correlated with substance abuse appears to be moderately heritable.

In work at the Center for Neurobehavioral Research on Addictions (CNRA), we examine mechanisms through which these maladaptive cognitive-behavior patterns contribute to SUDs. Our research includes the development and use of laboratory-based testing procedures to measure impulsivity, behavioral flexibility, attention to drug cues, and risky decision making. One example of this measurement approach capitalizes on a well-known psychological process known as the “Stroop” effect. The test paradigm requires subjects to respond as quickly as possible to stimuli (words) printed in different colors (red, green, or blue) by pressing one of three colored response buttons (red, green, or blue), corresponding the same color as the word. The individual is instructed to respond based on word color and ignore word content. Stimuli are presented in counter-balanced blocks of neutral words (e.g., couch, table, pencil) and drug-related words (e.g., crack, dealer, high). Individuals with cocaine dependence show a pronounced bias to cocaine (vs. neutral) words, measurable as a large reaction time difference (cocaine > neutral). In the natural environment, this attentional bias is believed to attract attention to drug-related stimuli, which initiates psychological craving and compulsive thinking about future drug use.

Neurochemically, key behavioral processes related to addiction are modulated by the monoamine systems (dopamine, serotonin, norepinephrine). Importantly, the monoamines are also strongly tied to the reinforcing effects of all known drugs of abuse; for example, there is extensive evidence linking dopamine activation to the reinforcing effects of psychostimulants like cocaine. Accordingly, one line of research in the CRNA is focused on modification of key behavioral processes through drugs that act on these neurotransmitter systems, including dopamine and serotonin. For example, previous CNRA research revealed that cocaine-dependent individuals treated with the selective serotonin reuptake inhibitor (SSRI) citalopram showed improved outcomes only if performance on a laboratory test of decision making was intact (within the range of healthy controls). Those with impaired decision making did not improve with citalopram treatment.

As noted in accompanying article by Dr. Schmitz, brain regions known to mediate key behavioral processes include thalamus, hippocampus, ventral striatum, amygdala, insula, and anterior cingulate, prefrontal, and orbital-frontal cortices. Efforts in addiction science are currently underway to identify the independent and integrated contribution of these brain regions to substance use disorders. A number of brain imaging modalities has been employed to investigate key behavioral processes in substance use. Using functional MRI (a technique to assess functional brain activity), studies at the CNRA and other laboratories have identified differential activation (vs. healthy controls) in anterior cingulate and prefrontal cortex related to attentional, working memory, and inhibitory control processes. Integrating data across several medication clinical trials for cocaine dependence, we found that thalamic activation predicted successful treatment response. Using diffusion tensor imaging (a technique used to mea-
has focused on dopamine-enhancing medications. We anticipate, for example, that these medications may ameliorate attentional bias to drug-related related stimuli as measured by the cocaine-stroop task described above. More ambitiously, using current statistical techniques we will attempt to synthesize neuroimaging, laboratory behavioral, and demographic factors in order to identify factor combinations ("latent" variables) that predict differential (and perhaps unique) paths to effective treatment outcomes in our pharmacotherapy trials.

About the Author
Scott D. Lane, Ph.D. is a Professor in the Department of Psychiatry and Behavioral Sciences and a member of the Neuroscience Program faculty in the Graduate School of Biomedical Sciences, both at the University of Texas Medical School at Houston. Dr. Lane directs the Neurobehavioral Laboratory at the Center for Neurobehavioral Research on Addictions (CNRA). His work utilizes techniques from behavioral psychology, psychophysics, and neuroimaging to address problems in substance abuse and other disorders of behavioral dysregulation.

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neuroimaging studies have linked these cognitive deficits to alterations in the anterior cingulate cortex (ACC) and orbitofrontal gyrus. Thus, emerging research offers a new understanding and appreciation of the role that cognitive processes may play in drug abuse and treatment.

A hallmark of drug abuse is the persistence of drug-taking behavior despite repeated and significant adverse outcomes. It is this apparent lack of response to negative feedback that renders the user with diminished control over their drug-taking behavior. On cognitive tasks involving learning and feedback, drug abusers consistently show poorer performance than non-drug control subjects. One such task, the Iowa Gambling Task (IGT), requires subjects to make a series of choices from decks of cards to try to maximize monetary payoffs. In virtually all published studies, clinical drug-abusing samples show a failure to learn or modify their choice behavior in favor of decks having better payoffs. Even in studies where subjects are given more information from which they could learn which decks had better payoffs, drug abusers fail to benefit. Poor decision-making as measured by the IGT overlaps conceptually with lack of planning, which is a critical component of impulsivity. Impulsivity has been defined as a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others. Performance on the IGT has been associated with performance on various response inhibition (impulsivity) tasks, with degree of impairment related to amount of past drug use.

Neuroimaging studies have implicated prefrontal regions to be related to decision-making and other cognitive deficits of substance users. In particular the functioning of the anterior cingulate cortex (ACC) has been shown to be hypoactive in drug users relative to drug-free controls. Responsivity of the ACC to cognitive errors appears to be related at least in part to dopamine, a neurotransmitter that also mediates the reinforcing effects of cocaine and other drugs of abuse. The diminished ACC response to errors does not appear to be due to lack of motivation, but rather impaired ability to detect errors and/or a failure of that detection to garner sufficient attention to lead to action in drug abusers. These findings demonstrate convincing drug abuse-related differences in neural systems that are generally accepted as central to at-

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is used widely and successfully for the treatment of Parkinson’s disease, where dopamine depletion is the cardinal neurochemical feature and cognitive functions that are mediated by prefrontal dopamine are often severely impaired. Whereas medications that enhance dopamine functioning have shown promise in the treatment of cocaine dependence (e.g., bupropion, disulfiram, methylphenidate, levodopa, dextroamphetamine), none of these studies incorporated cognitive testing to determine whether reductions in cocaine use were linked to cognitive improvement. To address this issue, we recently received a five-year grant from the NIDA to examine the efficacy of dopamine enhancement therapy that targets cocaine use and cognitive deficits by combining two dopaminergic medications: levodopa and ropinirole. By enhancing presynaptic dopamine release (levodopa) and postsynaptic D2 receptor function (ropinirole), the combined regimen is expected to jointly target dopamine deficits associated with chronic cocaine use and cognitive functions. It is hypothesized that treatment with the combined dopaminergic agents will improve abstinence outcomes, and that this will occur indirectly via improved performance on observed cognitive measures of decision-making, behavioral inhibition, reward motivation, and attentional bias (see parallel article). The proposed study will be the first of its kind to evaluate the effect of medication on specific cognitive tasks assessed at treatment entry and during treatment. By comparing the resolution of cognitive deficits to the reduction or elimination of drug use, the study is expected to offer new insights into a possible causal relationship of remediation improving treatment.

About the Author
Joy M. Schmitz, Ph.D. is a Professor in the Department of Psychiatry and Behavioral Sciences at the University of Texas Medical School at Houston. She directs the Treatment Research Clinic at the Center for Neurobehavioral Research on Addictions (CNRA), a National Institute on Drug Abuse (NIDA) Center of Excellence for medication development research. CNRA is a multi-disciplinary research group that focuses on advancing understanding and treatment of drug addiction. Co-Principal Investigators, Dr’s. Schmitz and Lane, recently received a five-year grant from NIDA to study cognitive remediation interventions for treatment of drug dependence.
The annual Neuroscience Research Center (NRC) reception was held on November 16, 2010 at the Annual Meeting of the Society for Neuroscience (SfN) in San Diego, CA.

Ernst Knobil Lecture
The Ernst Knobil Lecture featured Thomas Starzl, M.D., of the University of Pittsburgh, December 8, 2010.

Cooper Lectureship
The Cooper Lectureship featured Carol Tamminga, M.D., of The University of Texas Southwestern Medical Center at Dallas.

NRC 2010 Poster Session
Graduate students and postdoctoral fellows participating in the NRC sponsored Poster Session on December 4, 2010

NRC Poster Session Judges
LtoR front row: Raymond Grill, Ruth Heidelberger, Michael Stern, Jarek Aronowski, Daniel Felleman
back row LtoR Michael Beierlein, Neal Waxham, Fabrizio Gabbiani, Valentin Dragoi, David Marshak, Michael Beauchamp, and Andrew Bean, James McNew