Cocaine Abusers' Pretreatment Cue Responses Predict Recovery Success

In the future, patients' brain scans may help clinicians tailor addiction treatment to improve therapeutic outcomes.

BY LORI WHITTEN, NIDA Notes Staff Writer

A recent NIDA study strengthens prospects that brain imaging may one day help clinicians assign individual patients to treatment models that maximize their personal chances of a successful outcome. The study, conducted by Dr. Thomas Kosten and colleagues at Yale University School of Medicine, the University of Arkansas for Medical Sciences, and the Massachusetts Institute of Technology, correlated cocaine-addicted patients’ regional brain responses to drug cues with their outcomes in subsequent treatment. The patients whose brain scans revealed rapid and strong activation in sensory, motor, and cognition- and emotion-processing brain areas were more likely to drop out of treatment and fail to achieve stable abstinence.

"A test that predicts treatment outcomes, especially vulnerability to relapse, could help guide individualized treatment. For example, a clinician might recommend an extended stay in residential treatment or more intense behavioral intervention for patients with a propensity for relapse," says Dr. Kosten, now at Baylor College of Medicine.

Dr. Kosten and colleagues pursued the implications of an intriguing finding made in a prior study of cocaine cue responses: In some patients, strong, rapid activation of brain areas associated with emotion and sensing preceded the onset of craving. Although craving itself does not generally predict relapse, Dr. Kosten's team speculated that cue-induced brain activation that occurs quickly and reflexively, below awareness, might do so. They hypothesized that patients who showed such responses during the first 30 seconds of cue exposure would also demonstrate poorer treatment outcomes.

fMRI TRACKS CUE-INDUCED BRAIN ACTIVITY When cocaine-addicted patients watched a drug-related videotape, activation of the posterior cingulate cortex (highlighted in the brain image) occurred more quickly in those who subsequently relapsed.

To test their hypothesis, the investigators recruited 17 men and women who were participating in a trial of an antidepressant—sertraline—that is being...
evaluated as a possible treatment for cocaine addiction. The participants reported abusing cocaine 20 days, on average, during the month before the study. All met standard clinical criteria for cocaine addiction and had abused the drug for 6 years, on average. Most were new to treatment.

After being cocaine-free for 5 days, on average, each participant underwent functional magnetic resonance imaging (fMRI) while watching two 4-minute videotapes. The first minute of each tape reported on vegetable prices, and the participants' brain activity while hearing this emotionally neutral information served as a baseline for comparison. During the last 3 minutes, an actor pretended to smoke cocaine and experience a "rush." Immediately after viewing the tapes, each participant rated peak cocaine craving intensity on a scale from 0 to 10. After the imaging session, participants began taking either sertraline or a placebo daily and completed 2 weeks of residential treatment. During the 10-week outpatient phase of the trial, they were to continue their medication regimen, receive weekly individual cognitive-behavioral therapy, and submit urine samples three times a week.

INTERPLAY WITHIN CINGULATE CORTEX?

Nine of the 17 participants relapsed, defined by the investigators as submitting fewer than 15 of a possible 30 cocaine-free samples during the study and not completing outpatient treatment. Participants taking sertraline were just as likely as those taking the placebo to relapse. Relapsers and nonrelapsers reported cue-induced cravings of comparable intensity. The two groups differed, however, on brain activation during the first 30 seconds of the cocaine-cue videotapes. Relapsers showed greater cue-induced activation than nonrelapsers in several areas of the cortex: the left precentral (movement control), right superior temporal (auditory processing), right lingual and right inferior occipital (visual processing), and the left posterior cingulate cortices. The cingulate cortex is integral to attention, response inhibition, emotional regulation, and decisionmaking (see chart).

WHAT RESEARCHERS KNOW ABOUT THE CINGULATE CORTEX AND BEHAVIOR

The cingulate cortex connects to both the limbic systems (emotion and motivation) and the prefrontal cortex (planning and control of behavior) and seems to integrate emotion and cognition. The anterior and posterior regions of the cingulate are connected to different brain areas and differ functionally.

<table>
<thead>
<tr>
<th>Anterior Cingulate Cortex (ACC)</th>
<th>Posterior Cingulate Cortex (PCC)</th>
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<tbody>
<tr>
<td>Paying attention—The ACC monitors inputs from the senses (competing options) and selects what we attend to.</td>
<td>Responding reflexively—The PCC integrates sensory and movement information with established behavior patterns and acts &quot;below awareness.&quot; The PCC responds to reward and positive feedback.</td>
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<tr>
<td>Making decisions—Influenced by past experience, the ACC assesses risk, reward, and conflict. It works with areas of the frontal cortex to select a response.</td>
<td>Reacting emotionally—The PCC processes emotion-related autobiographical memories and the emotional perspective of self and others. Its activity correlates with internal physiological responses (heart rate, anxiety, and arousal level).</td>
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<tr>
<td>Inhibiting responses—The ACC integrates input from the prefrontal cortex and detects and corrects errors in behavior.</td>
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<tr>
<td>Detecting and controlling emotions—The ACC monitors what is going on inside (feelings, pain, and bodily arousal) and controls voluntary suppression of these sensations.</td>
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If researchers can determine changes in brain activity that predict responses to particular treatments, then clinicians could match therapy with individuals' scan results or even monitor progress in therapy."

If researchers can determine changes in brain activity that predict responses to particular treatments, then clinicians could match therapy with individuals' scan results or even monitor progress in therapy," says Dr. Kosten. More generally, studies that examine biological and behavioral predictors of treatment response elucidate the physiology underlying addiction—particularly the neural circuitry integrating stress, craving, and the propensity to relapse. New tools—for example, scanners that highlight brain areas that are working together—are expected to reveal more about these physiological processes. "With such functional connectivity imaging, one could examine how the anterior and posterior cingulate 'talk' to each other during a drug cue or other experience," says Dr. Rajita Sinha, an investigator in the Kosten study.

"Eventually, researchers will integrate the findings of such studies into a complete picture that will specify therapeutic pathways or help in the development of targeted medications to reduce relapse probability," adds Dr. Harold Gordon of NIDA's Division of Clinical Neuroscience and Behavioral Research.

SOURCE

researchers found that stress-induced craving was associated with a shortened interval to relapse following inpatient treatment, while hormonal responses to stress predicted the amount of cocaine the patients consumed during relapse.

The findings were reported in a followup to prior research conducted by Dr. Rajita Sinha and colleagues at Yale University School of Medicine. In the previous study, patients who listened to tapes reminding them of a stressful experience and a drug-related experience demonstrated an elevated biological stress response and increased cocaine craving compared with their response to tapes of relaxing experiences (see "Cocaine-Related Environmental Cues Elicit Physiological Stress Responses (Archive)").

Dr. Sinha and colleagues followed up with 49 of the 54 patients 3 months after completion of inpatient behavioral treatment. They found that patients who had experienced more intense cocaine craving while revisiting their stressful experiences via audiotape tended to relapse sooner. The probability of relapse 3 months after treatment was 56 percent among patients who reported no craving. Each unit increase on a craving intensity scale of 0 to 10 was associated with a 31 percent rise in the likelihood of relapse during the followup period.

Participants who released high levels of the stress hormones adrenocorticotropic hormone (ACTH) and cortisol in response to the stressful tapes consumed more cocaine than low-level responders during the followup. Three months after treatment, high-level responders had consumed about 8 g of cocaine cumulatively over their cocaine abuse periods, while low-level responders consumed about 3 g.

The findings of the study suggest that different components of the stress response are associated with various aspects of relapse: craving with reinitiating abuse and hormonal responses with the ability to control intake after reinitiating abuse. "Greater hormonal release during stress may 'prime' higher cocaine consumption or bingeing after return to abuse, perhaps by altering the rewarding effects of the drug," Dr. Sinha says.

Dr. Sinha and colleagues did not find a link between drug cue-induced craving and relapse outcomes, a result that is consistent with previous studies. However, because the drug cue imagery produced physiological reactions similar to those triggered by the stress cues, the researchers speculated that studies using a larger sample or exposure to actual drug cues, rather than just images of them, may show such an association.

Prior studies that did not find a link between cue-induced craving and relapse generally assessed only one or two dimensions of craving, Dr. Sinha points out. Studies that address multiple components—wanting the drug, feelings about the drug and about wanting it, drug-seeking behaviors, coping reactions, physiological arousal, and stress hormone levels—may better indicate vulnerability to relapse, she says.

"For people who are not addicted, knowing that you want a particular thing probably defines craving. Our findings suggest that for addicted people, craving is a 'state'—a multidimensional experience—comprised, in part, of stress-like arousal. In this state, desire becomes pathological, and people cannot delay gratification or divert their attention," says Dr. Sinha.

The results of Dr. Sinha's study suggest that stress-induced drug craving and physiological responses may be used as a diagnostic indicator of relapse propensity and might one day help clinicians tailor their interventions toward regulating stress and coping with stress-induced craving."Research on each component and the role that it plays in continued drug abuse is just beginning, but such studies ultimately may
improve our ability to help people attain long-term recovery," she says.

**SOURCE**

Drug Cues Induce Physiological Stress Responses in Cocaine-Addicted Patients

Cortisol levels, which normally decline in the morning, remain relatively high in cocaine-addicted patients after they listen to a five-minute tape of a stressful or drug-related experience, but not after they listen to a relaxing tape. Cue-induced elevations in cortisol and other stress hormones persisted for up to 30 minutes.

By Lori Whitten, NIDA NOTES Staff Writer

Overcoming addiction is in part a learning process, and people in recovery work to make and maintain healthy changes. In behavioral therapy, clinicians help patients learn techniques to avoid or navigate safely through experiences that evoke powerful urges to consume drugs: stressful situations and the people, places, and things the patient associates with past drug-taking experiences. Recent NIDA-funded research has demonstrated that cocaine-addicted patients respond to these drug-associated features in the environment as if they were stressful situations, with the release of adrenaline and other hormones that increase pulse rate and blood pressure, among other effects. The investigators also found that these responses of cocaine abusers take a long time to normalize, perhaps indicating that the drug heightens sensitivity to stress.

Dr. Rajita Sinha and colleagues at the Yale University School of Medicine in New Haven, Connecticut, conducted their study with 54 cocaine-addicted men and women, aged 21 to 50, at an inpatient research facility. Before entering treatment, the patients had abused cocaine for an average of 9 years; immediately prior to treatment, they had, on average, consumed the drug 3 or more times per week and spent $224 weekly to buy the drug. Almost all (94 percent) consumed cocaine in its smoked form (crack). Each patient had been abstinent for 2 weeks prior to the laboratory sessions.

To study physiological and emotional responses to stress and cocaine-related cues in the laboratory,
the investigators drew on the patients' individual experiences. They elicited from each patient detailed accounts of three past personal experiences: one very stressful, one relaxing, and one specifically related to taking cocaine. From each patient's stories, the researchers created three tape recordings that would, when played back, rekindle his or her feelings of stress, relaxation, and cue-induced craving (see "Reliving A Stressful Situation: Excerpt From a Guided Imagery Tape"). To enhance the strength of the responses, the researchers trained the patients in guided imagery—how to relive a scene mentally while listening to a tape, as if it were happening at that moment.

Each patient participated in three 3-hour testing sessions. Throughout each session, the patient sat on a hospital bed wearing headphones, an intravenous catheter in one arm for drawing blood, a blood pressure monitor on the other arm, and a pulse sensor on one finger. For the first hour, an adaptation period, the patient practiced tape-guided progressive relaxation while periodically reporting anxiety and craving levels. Next, the patient heard one of the 5-minute tapes based on his or her own experiences, introduced with a message to "Close your eyes and imagine yourself in the following situation." Over the three testing sessions, conducted on different days, the

Craving, and Anxiety in Cocaine-Addicted Patients
The patient relived all three of his or her stressful, drug-related, and relaxing experiences. When the tape finished, the patient rated the vividness of the scenes and his or her cocaine craving and anxiety. A nurse monitored the patient’s pulse and blood pressure and drew blood samples periodically during the testing and for 75 minutes after the tape ended.

The researchers found similar responses to the stressful and drug-related tapes. Patients' pulses increased and their blood pressure rose while they listened to both. Blood levels of biochemicals involved in the stress response—including noradrenaline, cortisol, prolactin, adrenocorticotropic hormone, and adrenaline—were elevated when participants listened to stressful and drug-related tapes compared with when they listened to the relaxing tapes. Stressful and drug-related tapes also increased participants' subjective responses—craving and anxiety—compared with the relaxing tapes.

The stress responses generated in the study were in keeping with previous laboratory studies with cocaine abusers, says Dr. Sinha. "Stress reactions after both the stressful and drug-related tapes in this study were similar to or higher than those observed when researchers have used other techniques to induce stress—for example, requiring..."
Cocaine-addicted patients showed greater arousal and increased pulse and biochemical stress response, as well as increased craving and anxiety, when they mentally relived a 5-minute stressful or drug-related personal experience than when they listened to relaxation tapes. Arousal persisted for up to 30 minutes after the imagery stopped.
Brain Response Differs in Men and Women During Cue-Induced Craving

By Lori Whitten, NIDA NOTES Staff Writer

Some aspects of cocaine addiction and recovery are different for men and women—including the reasons for seeking drug rehabilitation, response to treatment, and vulnerability to relapse. Women are more likely to seek cocaine abuse treatment in response to co-occurring depression, remain abstinent after treatment, and relapse in response to interpersonal problems and negative feelings. Cocaine-addicted women also demonstrate greater craving than men in response to drug cues. In the first brain imaging study of cocaine craving by cocaine-addicted women, NIDA-funded researchers have made observations that, if borne out in larger studies, may point to neurological sources of these differences.

Dr. Clinton Kilts and colleagues at the Emory School of Medicine in Atlanta used positron emission tomography (PET) to measure drug-craving-related changes in regional cerebral blood flow—a correlate of neural activity—in eight cocaine-addicted African-American women aged 35 to 46. The women had abstained from cocaine use for 1 to 14 days and reported frequent periods of cocaine craving in the 30 days preceding the study. While lying in the PET scanner, each woman listened to a 1-minute recording of a script describing her personal experiences of acquiring the drug and anticipating sensations associated with taking cocaine. Each patient’s script was derived from her own answers to an autobiographical questionnaire and narrated in the first person:

"...I start thinking about how good it’s going to feel to take that first hit...with my eyes wide open I take my lighter out of my pocket, put it to the stem, and get ready to take that first, good blast...."

The researchers injected each woman with a radiotracer and took pictures of the blood flow in her brain as she listened to the script and relived the scene in her mind. After each brain scan, the women rated the urge to use cocaine, vividness of the mental image, and their emotions. They repeated this process twice.

The women also underwent imaging in three control situations: resting, listening to a script of a personal experience in nature, and listening to a script designed to provoke anger. The researchers verified that the mental imagery of the cocaine-related script induced a greater urge to use cocaine than the nature or anger script. By comparing the brain scans produced in response to the different scripts, the researchers were able to evaluate cerebral blood flow while the women were craving cocaine versus when they were relaxed and not thinking of the drug. The procedure also distinguished changes related to craving from those that might simply reflect strong general emotional reactions (as in the anger-inducing script). To examine possible sex differences in the neural representation of cocaine craving, the investigators compared the findings in women with results from eight cocaine-addicted men of similar ages and backgrounds who experienced the same process.

In both men and women, cue-induced cocaine craving activated several brain areas involved in determining a cue’s reward value and controlling reward-related behaviors, including the right nucleus accumbens—a structure that seems to produce the expectation of
These PET scans show differences in blood flow between a neutral state and a cocaine-craving state. White areas indicate an increase in blood flow. Most notable is the decrease in blood flow in the women's amygdala (top right panel) during craving; men show an increase in blood flow during craving (bottom right panel).

Selected Key Brain Regions Affected by Cue-Induced Cocaine Craving in Cocaine-Addicted People

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Putative Role in Behavior</th>
<th>Activity Changes During Cocaine Craving</th>
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<tbody>
<tr>
<td>Right nucleus accumbens</td>
<td>Processes anticipated and attained rewards—probably contributes to the expectation of pleasure during craving</td>
<td>Increased activity, Increased activity</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Generates and regulates emotional responses; assesses the positive or negative value of experiences and forms associations between experiences and emotional consequences</td>
<td>Increased activity, Decreased activity</td>
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<tr>
<td>Dorsal anterior cingulate cortex</td>
<td>Monitors competing options, inhibits goal-inappropriate behavior, and plans movements related to obtaining rewards; activity influenced by past experiences—possibly provides cognitive control of drug-seeking behavior</td>
<td>Increased activity, greater than that of men</td>
</tr>
<tr>
<td>Ventral anterior cingulate cortex</td>
<td>Regulates emotional response to cocaine cues; activation may precede craving onset</td>
<td>Increased activity, Increased activity, less than that of men</td>
</tr>
</tbody>
</table>
Frontal cortex | Monitors relationship of drug cue to drug availability; provides inhibition or control over actions; activity influenced by past experiences—possibly counterregulates emotional input | Increased activity | Increased activity, greater than that of men

"As a field, we need more and better controlled studies of sex differences in factors that cause relapse," says Dr. Kilts. Combining imaging technologies in the same study—for example, PET with magnetoencephalography—would improve the localization of neural activity. "We could better define the neural responses that occur before, during, and after drug cues—illuminating the temporal sequence of the craving experience in men and women," he says.

"This research reveals that men and women differ in a critical brain area in their responses to cocaine craving," says Dr. Steven Grant of NIDA’s Division of Clinical Neuroscience, Development, and Behavioral Treatments. "Differences in the amygdala may indicate that male and female abusers crave the drug for different reasons or hope to achieve different results from taking the drug. Imaging studies that examine gender differences in specific behavioral aspects of drug craving will provide insight on how to tailor treatment programs to meet the needs of men and women."

**Source**