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Investigators Show Nicotine Primes Brain for Cocaine Use

Contributing faculty for this article: **Denise B. Kandel, PhD, and Eric R. Kandel, MD**

Among adults aged 18 to 34 who used cocaine at least once, more than 90 percent smoked cigarettes first. It's also long been known that use of one addictive substance increases the risk of another, such as cigarette smoking and consumption of alcohol before use of cocaine or marijuana — the so-called "gateway sequence." Now, for the first time, neuroscience researchers at Columbia University College of Physicians and Surgeons have shown that nicotine primes the brain for cocaine use, and they identified a molecular mechanism underlying this gateway sequence.

"These results show nicotine creates fundamental changes in the brain that increase the effects of cocaine entering the brain," explains Denise B. Kandel, PhD, Professor of Sociomedical Sciences in Psychiatry at Columbia. Dr. Kandel conducted the study, which was published in *Science Translational Medicine*, with Eric R. Kandel, MD, University Professor, Fred Kavli Professor and Director, Kavli Institute for Brain Science at Columbia and a Howard Hughes Medical Institute Senior Investigator, and lead author Amir Levine, MD.

"Our study shows it is possible to take complex epidemiological phenomena and evaluate them in animal models," adds Dr. Eric Kandel. "This study is the first to pinpoint the mechanism underlying the effect of nicotine on cocaine use on a behavioral level, on a cellular/physiological level, and on a molecular/genetic level. The concept of one agent altering the response of the brain to a second agent is called meta-plasticity."

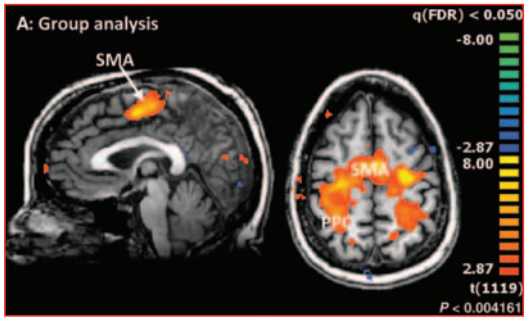
see Nicotine Primes Brain for Cancer Use, page 4

Elucidating Cognitive Function in Severely Brain-Injured Patients

Contributing faculty for this article: **Nicholas D. Schiff, MD, and Henning U. Voss, PhD**

Adapting a novel neuroimaging technique to assess capacity to communicate and establish direct communication with brain-injured subjects with impaired motor function was the focus of a study published in the March 2011 issue of *Brain* by researchers at Weill Cornell Medical College.

"The use of functional MRI-based paradigms to specify levels of residual cognitive capacity, as well as the extent to which they have a clear relationship to traditional bedside evaluations, are still major open questions," says Nicholas D. Schiff, MD, the Jerold B. Katz Professor of Neurology and Neuroscience and Professor of Public Health at Weill Cornell Medical College and a neurologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. Dr. Schiff and his research team tested a hierarchical, single-response-type, functional MRI (fMRI) methodology – previously validated in normal subjects – to provide assessments of the subjects' capacity to utilize brain activity to follow commands and answer questions with graded levels of difficulty, as well as to minimize their efforts and afford the greatest flexibility for response output.



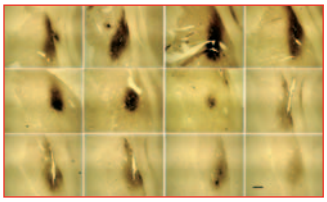
Group analysis of the command-following task in normal subjects. The nine subjects imagined themselves swimming. Areas of activation are predominantly in the supplementary motor area, partially extending laterally into the premotor areas, and parts of the posterior parietal cortex. (x = 2 mm, z = 48mm lin Talairach space).

see Brain-Injured Patients, page 3

Can Gene Therapy Change the Landscape of Treatment for Parkinson's Disease?

Contributing faculty for this article: **Blair Ford, MD**

More than 1.5 million people in the United States are affected by Parkinson's disease. At present, there is no cure nor is there any effective neuroprotective agent available to slow or halt the progression of the disease. A novel study that is much anticipated by the Parkinson's disease community is now underway at NewYork-Presbyterian Hospital/Columbia University Medical Center and 10 other leading medical centers around the country.



Neurturin growth factor is expressed at injection site at treatment with gene therapy.

The Phase 2/3 clinical trial involves an experimental therapy – CERE-120 – that may prevent the death of dopamine neurons in patients with Parkinson's disease (PD). CERE-120 is composed of an adeno-associated virus vector carrying the gene for neurturin, a naturally occurring protein – also known as a neurotrophic factor – to repair damaged and dying dopamine-secreting neurons.

"CERE-120 therapy is the only gene therapy currently in clinical trials that delivers a nerve growth factor with the potential to slow down the progression of Parkinson's," says Blair Ford, MD, Professor of Clinical Neurology and the principal investigator of the study at NewYork-Presbyterian/Columbia. "Other gene therapies currently under investigation aim to reduce Parkinson's symptoms but are not designed to help prevent the death of nerve cells in the brain."

The experimental therapy attempts to protect nerve cells by delivering the gene for neurturin directly to the brain. In laboratory experiments, neurturin was shown to repair damaged nerve cells, restore their function, and help keep them alive. In animal models of Parkinson's disease, it has been shown that forcing cells to generate huge amounts of GDNF (glia-derived neurotrophic factor) appears to both protect neurons and prevent the development of PD, providing a rationale for moving into human studies.

According to Dr. Ford, a unique aspect of the trial is that the patient is not given the treatment substance itself, but rather the gene to make the substance. "The gene is injected into the brain of patients with PD using the virus that 'transfects' brain cells, turning cells into miniature factories for neurturin, a synthetic version of GDNF, the growth factor for dopamine-producing cells," explains Dr. Ford. "In Parkinson's disease, the brain's dopamine cells are dying for reasons unclear. As part of normal development in the human brain, dopamine cells are supported by GDNF. Therefore, providing this nerve growth factor or its analog seems, at least at face value, promising if it can be accomplished technically."

see **Treatment for Parkinson's Disease,** page 3

NewYork-Presbyterian/Westchester Receives Planetree Designation

NewYork-Presbyterian Hospital's Westchester Division is the first behavioral health hospital in the nation to be formally named by Planetree Inc. as a "Planetree Designated Patient-Centered Hospital."

"Patient-centered care is central to everything we do, and it is particularly important in a behavioral health setting," says Philip J. Wilner, MD, MBA, Vice President and Medical Director of Behavioral Health at NewYork-Presbyterian Hospital/Weill Cornell Medical Center and Professor of Psychiatry at Weill Cornell Medical College. "Creating an environment where patients feel respected and creatively engaged in their recovery promotes healing."

Since becoming a Planetree member in 2003, NewYork-Presbyterian/Westchester has enhanced its environment in a number of ways, including:

- renovations of the main entrance to include a welcome desk, cozy seating area, chapel, patient resource library, and small café
- renovated courtyards, enhanced landscaping, and a labyrinth for meditation and reflection
- cultural programs and an in-house gallery displaying patient artwork
- new menus and patient involvement in food preparation and cooking groups
- alternative and complementary medicine, such as aromatherapy and pet therapy

"The Planetree Designation is the only award that recognizes excellence in person-centeredness across the continuum of care," says Susan Frampton, President of Planetree Inc. "The designation signals to health care consumers that NewYork-Presbyterian/Westchester is a hospital where providers partner with patients and families, and where patient comfort, dignity, empowerment, and well-being are prioritized with providing top-quality clinical care."

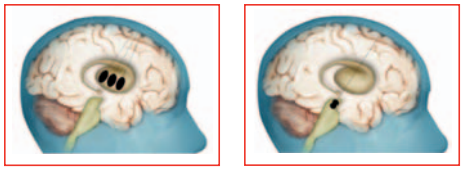
Designated hospitals are also nationally recognized by The Joint Commission, which has approved the designation program as one of the awards recognized on its Quality Check website in the special quality awards section.

NewYork-Presbyterian Hospital/Westchester Division is located in White Plains, New York, a suburb of New York City.

continued from **Treatment for Parkinson's Disease** page 2

Results from a previous study published in the journal *Lancet Neurology* (Marks et al., 2010) suggest small improvements in Parkinson's symptoms when CERE-120 is injected into only one part of the brain. "In the preliminary Phase 1 studies," notes Dr. Ford, "although CERE-120 was found to be safe, it was not found to be effective. However, examination of the brains of two patients in the initial cohort who died of unrelated causes in the years following the study showed evidence that the gene therapy technique had worked. After injection, the CERE-120 gene was successfully incorporated into the brain cells, and the cells began to produce large quantities of neurturin. Knowing that the principle was sound and the technique was effective provided further impetus to carry out a Phase 2 study, with a slight modification in technique."

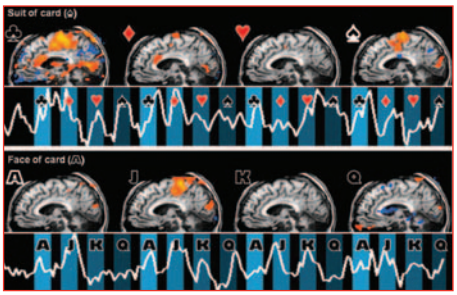
In the current Phase 2 study, neurosurgeons inject CERE-120 into two regions of the brain most affected by Parkinson's, the substantia nigra and the putamen. There are four main injection sites, targeting the whole area where dopamine brain cells are located and where they project to. Once in the brain, the neurturin gene should begin producing a steady supply of neurturin. This new approach intends to expose both ends of the dopamine neurons to neurturin and will hopefully halt progression of the disease.



Two targets for gene therapy: Putamen (left) and Substantia Nigra

Dr. Ford cautions that CERE-120 is still experimental and comes with risks, including those associated with neurosurgery. Viral vectors similar to that used in CERE-120 have been used in many other experimental gene therapies and have not caused serious side effects or disease, but there still may be unknown risks. The study will enroll approximately 50 patients with early Parkinson's disease. More information about the study, including ways to enroll, is available in the clinicaltrials.gov study registry.

continued from **Brain-Injured Patients,** page 1



Multiple choice communication task results from a clinical subject who picked the Ace of Spades card. The subject responded with swimming imagery. The time course represents the blood-oxygen-level-dependent signal in the supplementary motor area cluster (suit) and the posterior parietal cortex (face), each in the region with the strongest blood-oxygen-level-dependent response. The symbols next to the brain indicate the used contrast for generating the SPM [club, diamond, heart, spade (suit) and ace, jack, king, queen (face)].

The researchers studied a control group of 14 normal subjects and seven severely brain-injured patients who ranged in function from a minimally conscious state to locked-in syndrome, looking at how the brains of these patients responded to a set of commands and questions while being scanned with fMRI.

The paradigm began with a command-following task in which the control volunteers were asked to imagine performing their favorite sports, the patients to imagine themselves swimming. This command formed the basis for further communication. Next, the three patients who could do this, and all of the controls, were asked to use the same imagined activity to respond to one of two options in a simple two-part question. The researchers then introduced a multiple-choice task in which all normal subjects picked and four of the clinical subjects were taught one of the face cards from a deck of playing cards before the MRI scan. They were then asked to respond again using the imagined physical activity when either the correct face or suit of their selected card was named during the scan.

The findings showed a wide, and largely unpredictable, variation in the ability of patients to respond to a simple command and then, using that same command, to answer simple yes/no or multiple-choice questions. This variation was apparent when compared with their ability to interact at the bedside using voice or gesture. Some patients unable to communicate by gestures or voice were unable to do the mental tests, while others unable to communicate by gestures or voice were intermittently able to answer the researchers' questions using mental imagery. And, intriguingly, some patients with the ability to communicate through gestures or voice were unable to do the mental tasks.

"The study tested three levels of communication in steps that required increasing cognitive capacity," says Hemming U. Voss, PhD, the study's senior investigator and Associate Professor of Physics in Radiology at Weill Cornell Medical College. "While we could not unambiguously establish communication in these brain-injured patients, our research is helping us identify problems specific to this patient population. We got a clear picture about where and how to look for this kind of brain activity in response to certain commands."

"We have to abandon the idea that we can rely on a bedside exam in our assessment of some severe brain injuries," says Dr. Schiff, the study's corresponding author. "These results demonstrate that patients who show very limited responses at the bedside may have higher cognitive function revealed through fMRI."

While progress has been made in elucidating the range of brain function in those who are severely injured, Dr. Schiff urges caution. "Although everyone wants to use a tool like this, fMRI is not yet capable of making clear measurements of cognitive performance. There will be a range of possible responses reflecting different capabilities in these patients that we have to further explore and understand. Collecting large samples of data within and across brain-injured subjects will be necessary to calibrate these methods for further development and clinical uses."

Going forward, the research group, along with others in the field, is planning a major multicenter trial of fMRI along with European and Canadian colleagues supported by The James S. McDonnell Foundation to better understand both its promise and limitation in gauging cognitive abilities in severely brain-injured patients.

For more information, see the original journal article: Bardin JC, Fins JJ, Katz DI, Hersh J, Heier LA, Tabelow K, Dyke JP, Ballon DJ, **Schiff ND, Voss HU**. Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. *Brain*. 2011 Mar;134(Pt 3):769-82.

continued from **Investigators Show Nicotine Primes Brain for Cocaine Use,** page 1

Using a novel mouse model, the research team explored the effects of sequential administration of nicotine and cocaine on behavioral responses, synaptic plasticity, and gene expression, as well as acetylation of histones in the promoter regions of genes in the striatum, a brain region critical for addiction-related reward. Nicotine was administered to the mice in their drinking water, while cocaine was given via injection.

The investigators found that pretreatment with nicotine for seven days increased the response to cocaine. For example, locomotor sensitization was increased by 98 percent and conditioned place preference (CPP) by 78 percent. CPP, a measure of the amount of time an animal spends in compartments previously associated with stimulus or reward, is a well-established measure of drug-induced conditioning and a naturalistic model of addictive behavior.

Nicotine also accentuated the reduction in long-term potentiation in the nucleus accumbens by 24 percent. The nucleus accumbens is a region of the brain where drug-related increases in dopamine are associated with reward.

Molecular studies showed that nicotine rewires the brain's response to cocaine by boosting expression of *FosB*, an immediate response gene implicated in addiction to many drugs of abuse and in the response to other rewarding stimuli. Nicotine also inhibited histone deacetylase, causing global histone acetylation in the striatum. Conversely, giving the mice low doses of theophylline, an asthma drug which also stimulates histone deacetylase, attenuated the response to cocaine.

The priming response was unidirectional, occurring only when nicotine was given first. Administering cocaine first did not change the behavioral response of the mice to nicotine or the expression of *FosB*. Moreover, the two drugs needed to be given in close sequence to produce the changes observed, since the priming effect only occurred when cocaine administration partially overlapped with nicotine exposure.

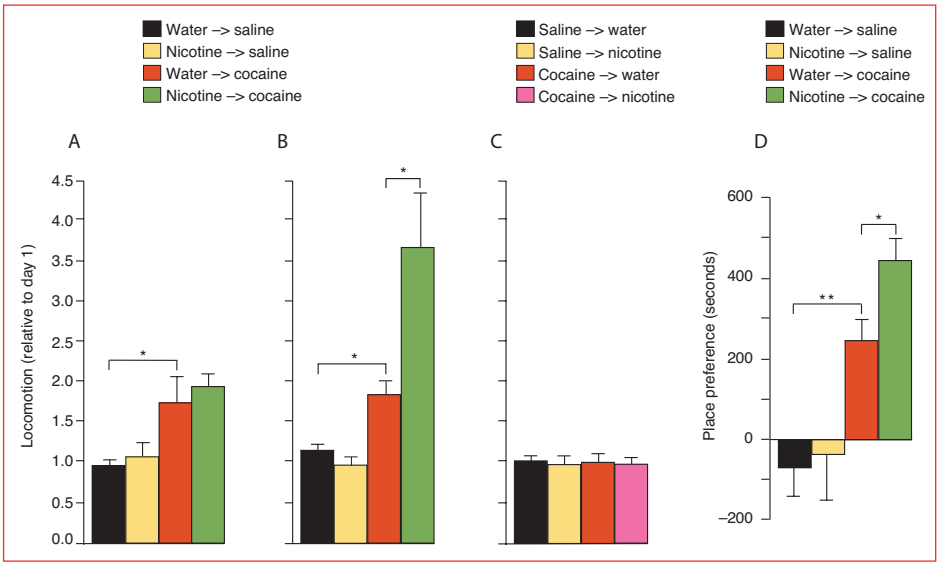
To extrapolate the results to humans, the scientists analyzed the sequence of cocaine and cigarette use among participants in the National Epidemiological Study of Alcohol Related Consequences, a cohort representative of the U.S. population. They found that the rate of cocaine dependence was greatest among those who began using cocaine after having smoked cigarettes and while they were still smoking (20.2 percent); the rates of dependence were much lower among those who initiated cocaine before smoking (6.3 percent) and those who had ever smoked fewer than 100 cigarettes (10.2 percent).

The data also signal concerns about the use of nicotine replacement therapy among cocaine abusers who wish to stop smoking, since the nicotine may fuel their cocaine addiction. Alternative medications or behavioral smoking cessation approaches may be warranted in this group.

The data also signal concerns about the use of nicotine replacement therapy among cocaine abusers who wish to stop smoking, since the nicotine may fuel their cocaine addiction.

The animal model and sequence of experiments they employed can also be applied to the study of other substances for which epidemiological data suggest a gateway sequence. For example, the investigators have already initiated similar animal studies to see if alcohol primes the brain for cocaine use.

"These findings emphasize the need for developing more effective public health prevention programs for all products that contain nicotine, especially those targeted toward young people," the investigators concluded. "Our data suggest that effective interventions would not only prevent smoking and its negative consequences, but could also decrease the risk of progression to chronic illicit drug use."



Nicotine priming enhances cocaine-induced behavioral endpoints, sensitization, and conditioned place preference (CPP). (**A** and **B**) For sensitization, we treated mice with nicotine (50 μg/ml) in the drinking water for either 24 hours (A) or 7 days (B). For the subsequent 4 days, the mice were treated with a single cocaine injection per day (20 mg/kg), with continued exposure to nicotine in the drinking water (n = 10 to 15 per group). Data expressed as total distance traveled on day 4 compared with day 1. (**A**) Lack of effect of 24 hours of nicotine treatment on cocaine-induced locomotion. (**B**) Effect of 7 days of nicotine treatment on cocaine-induced locomotion. (**C**) Lack of effect of 7 days of cocaine treatment on nicotine-induced locomotion. (**D**) Effect of nicotine pretreatment on CPP. After 7 days of exposure to nicotine, mice were conditioned to either side of the place preference chamber with cocaine or saline. Preference scores were calculated by subtracting the time spent in the cocaine-paired side after conditioning from the time before conditioning (n = 8 per group). Data represent means ± SEM. *P < 0.05; **P < 0.01.

For more information, see the original journal article: Levine A, Huang Y, Drisaldi B, Griffin EA Jr, Pollak DD, Xu S, Yin D, Schaffran C, **Kandel DB, Kandel ER**. Molecular mechanism for a gateway drug: epigenetic changes initiated by nicotine prime gene expression by cocaine. *Science Translational Medicine*. 2011 Nov 2;3(107):107ra109.

The Marshmallow Test for Delayed Gratification: 40 Years Later

Contributing faculty for this article: **B.J. Casey, PhD**

B.J. Casey, PhD

A landmark study in the late 1960s and early 1970s conducted by Walter Mischel, PhD, Niven Professor of Humane Letters at Columbia University, used marshmallows and cookies to assess the ability of preschool children to delay gratification. If they held off on the temptation to eat a treat, they were rewarded with more treats later. Some of the children resisted, others didn't. A newly published follow-up revisits some of the same children, now adults, revealing that these differences remain: Those better at delaying gratification as children remained so as adults; likewise, those who wanted their cookie right away as children were more likely to seek instant gratification as adults.

The current research, led by B.J. Casey, PhD, Director of the Sackler Institute and the Sackler Professor of Developmental Psychobiology at Weill Cornell Medical College, assessed the behavioral and neural correlates of delay of gratification in almost 60 adults who participated as four-year-olds in the original delay-of-gratification task and whose self-control abilities remained consistent in follow-up assessments. "In the present study, we examined the extent to which individual differences in delay of gratification assessed when participants were in preschool and in their 20s and 30s predicted control over impulses and sensitivity to social cues at the behavioral and neural level when the participants were in their 40s," explains Dr. Casey.

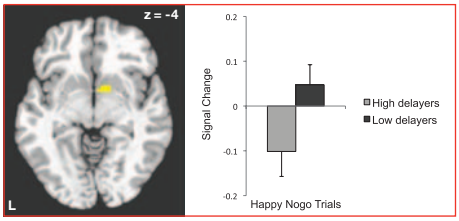
The individuals represented either extreme of the delayed-gratification spectrum – high delayers and low delayers. Two experiments were conducted to investigate their ability to refrain from responding to alluring cues.

In the first experiment, participants were tested on "hot" and "cool" versions of an impulse control task (i.e., the go/nogo task). Because marshmallows and cookies can be less enticing to adults, the researchers substituted the treats for social cues of faces with emotional expressions that over a lifetime come to have positive value. In the "cool" test, participants looked at a screen displaying a series of faces with neutral expressions and were asked to press a button whenever one gender appeared (go), but not to the other (nogo). The go cue occurred frequently, making it more difficult to stop for the rare nogo cue. This test revealed no significant differences between the two groups. A second, "hot" test used emotional cues such as a happy or frightened face. Individuals who were less able to delay gratification as children (low delayers) performed more poorly than did high delayers when having to stop to the positive social cue of a happy face but not to a neutral or fearful face.

"Over a lifetime, smiling faces come to be associated with positive outcomes and have been shown by our group to influence behavior as much as food or money," notes Dr. Casey. "The positive social cue interfered with the low delayer's ability to suppress his or her actions. The people who couldn't delay as four-year-olds, when 40, couldn't stop themselves from reacting to positive social cues. It's really shocking 40 years later to see such a consistency in the behavior. A lot happens in life between four and 40."

In a subset of the study cohort, the second test was then repeated while the participant's brain was scanned using noninvasive functional magnetic resonance imaging (fMRI). Specifically they tested for differences between the low and high delayers when inhibiting a response to positive social cues. The results showed that the brain's prefrontal cortex, a region involved in rational thoughts and actions, was more active for high delayers, and the ventral striatum – an area linked to rewards and risk taking – was more active in low delayers.

According to Dr. Casey, who is a pioneer in novel uses of brain imaging to examine behavioral and brain development, "This is the first time we have located the specific brain areas related to delayed gratification. These findings could have important implications for substance abuse and obesity, which have been related to delay ability in previous studies. By finding ways to cool down cues that may drive these behaviors, we may be able to ultimately prevent these behaviors."



Low delay ability in early childhood predicts greater ventral striatal activity when inhibiting responses to positive social cues 40 years later. **Left:** Activation map for the three-way interaction of task, emotion, and delay group depicting ventral striatum activity thresholded at $P < 0.05$, small volume corrected, displayed on a representative high-resolution T1-weighted axial image. **Right:** Ventral striatal response to happy "nogo" trials in high and low delayers.

Research in the field has shown that "higher delay ability promotes the development of better social, cognitive, and emotional coping in adolescence and buffers against the development of a variety of dispositional physical and mental health vulnerabilities in middle age, such as higher body mass index, sensitivity to rejection, cocaine/crack use, and marital divorce/separation."

"Our findings provide a neurobiological basis for differences in this ability," says Dr. Casey. But, she emphasizes, the inability to delay gratification is not a fatal flaw. "The high delayers who were able to exploit the situation and thus receive two cookies may be more methodical and thoughtful in their actions, while low delayers who act in the moment may be more likely to be risk takers and pioneers, and we need both in society."

Casey BJ et al. Behavioral and neural correlates of delay of gratification 40 years later. *Proceedings of the National Academy of Sciences USA*. 2011 Sep 6;108(36):14998-5003.

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