PET Study Reveals Brain Activation Differences

Cocaine addicts have an increase in activity after methylphenidate exposure, nonaddicts a decrease.

BY KERRI WACHTER Senior Writer

PHILADELPHIA — The activation of certain regions of a drug addict’s brain following drug use may shed light on the compulsive nature of addiction, according to data presented at the annual meeting of the Society of Nuclear Medicine.

Using 18F-fluorodeoxyglucose PET imaging, researchers at Brookhaven National Laboratory in Upton, N.Y., found that cocaine addicts have an increase in brain activation in the orbitofrontal cortex after exposure to methylphenidate, which is similar in effect to cocaine. In contrast, healthy control subjects in the study had a decrease in activity in the same region, said Nora D. Volkow, M.D., lead researcher and director of the National Institute on Drug Abuse, Rockville, Md. “They’re going in opposite directions. This becomes very significant.”

The difference in the response to methylphenidate suggests that abnormal recruitment of the orbitofrontal cortex— which is involved with salience, attribution, motivation, and drive—may reinforce the saliency of the drug. Moreover, this region is associated with compulsive behaviors, so its abnormal activation could underlie the compulsive drug intake that occurs in addicted subjects,” Dr. Volkow said.

In the study, brain metabolism was measured in 21 cocaine-addicted men and 15 nonaddicted men as controls. All subjects underwent two PET scans. Both groups were imaged following two sequential patterns: 1) Abuse and following two sequential doses of methylphenidate—0.5 mg/kg, and 0.25 mg/kg—given intravenously 90 minutes apart. The investigators used two sequential doses because cocaine abusers “do not take drugs in isolation—they do it compulsively,” Dr. Volkow said.

Methylphenidate was chosen because, like cocaine, it blocks dopamine transporters. In addition, cocaine users report that methylphenidate's effects are similar to those of cocaine.

Cocaine abusers were an average of 36 years old and met the DSM-IV criteria for cocaine dependence. They used 3 g of cocaine per week, with continuous use for at least 6 months prior to the study, and averaged 13 years of use.

In reports of findings of being high, control subjects had a greater response to the first dose than the second dose. Cocaine abusers also reported a greater high with the first dose, but the magnitude of their response was much lower than for the control subjects, she said.

In self-reports of craving, the control subjects reported very little craving for expected placebo. In contrast, the first methylphenidate dose induced very strong cravings in the cocaine users and the second (and lower) dose induced cravings that were still strong.

When the researchers specifically compared the differences in brain metabolic response between placebo and methylphenidate, cocaine abusers had a significant increase in metabolism in the right orbitofrontal cortex, while normal subjects had a decrease in metabolism. For the cocaine abusers, increased activity in the right orbitofrontal cortex corresponded well with self-reports of cocaine craving.

“These findings lend credence to the hypothesis that the orbitofrontal cortex and anterior cingulate gyrus play a major role in the manifestation of drug addiction.”

Both of these regions are important in assigning salience to stimuli and also in exerting inhibitory control,” Dr. Volkow said.

In a related study, researchers looked at the effect of expectation on brain activity in nonaddicted subjects. Twelve healthy subjects with minimal prior drug experience (average age 13 years) were imaged using fluorodeoxyglucose PET under four conditions: the subject expected placebo and received placebo (baseline); the subject expected methylphenidate and received placebo; and the subject expected methylphenidate and received methylphenidate. The order of the conditions was randomized for each patient. A dose of 0.5 mg methylphenidate was given intravenously 5 minutes prior to the PET scan.

Self-reports of high and drug effects from the subjects corresponded well with methylphenidate use, regardless of expectation. There was in increase in glucodynamic metabolism, particularly in the cerebellum, when methylphenidate was given, regardless of whether or not it was expected.

With the administration of unexpected methylphenidate, cocaine abusers experienced increases in metabolism in the right frontal cortex. However, the expectation of methylphenidate alone activated the orbitofrontal cortex, Dr. Volkow said.

“These findings suggest that the orbitofrontal cortex by expectation alone suggests this region is involved in the processing of unexpected stimuli,” she said.