RESPONSE: IMAGES AND INTERVENTIONS

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Paul Linde: As a clinician, one message I take away from the imaging information is that methamphetamine and cocaine cause frontal lobe dysfunction, resulting in damage to decisionmaking, judgment, and impulse control. All of these play a role in relapse as well. We can educate people about this and about staying abstinent to try to protect their brains from further injury.

Linda Chang: Not only protect the brain from further injury, but also give it time to heal. We don't know how much of the damage drugs do is permanent. For example, in the past, we assumed that when you see a decreased dopamine transporter density on the PET scan, those dopamine neurons are permanently impaired or gone. But Nora Volkow and I found that after a group of methamphetamine abusers were abstinent for a long period—more than 6 or 12 months—their dopamine transporter levels started to improve. This suggests that if you stop using the drug for long enough, the brain cells can actually recover. Gene-Jack Wang also published a PET study that found more normal brain function in former methamphetamine abusers who had been abstinent for a long time than in those who were still in early abstinence (Wang et al., 2004).

Even when there is permanent damage, the brain may find ways to compensate. In fact, this happens in all forms of brain injury. My colleagues and I have done functional MRIs in patients with HIV-related brain injury and observed that when one part is not working well, the brain uses its reserves or other parts to maintain its function. It's only when the reserve capacity is exhausted that they then develop cognitive deficits or impairments.

There is an emerging literature showing that cognitive-behavioral therapy may reroute brain function to maintain or restore lost capacity. Patients who have decisionmaking or impulse control or other problems may learn to tap into parts of the brain they haven't used in the past.

Linde: Among my patients, who are mainly recovering methamphetamine and cocaine abusers, the cognitive and motor issues seem minor compared with mood problems. There also is a clear subset of patients who essentially develop low-grade schizophrenia after prolonged methamphetamine abuse, particularly those who have taken the drug intravenously for a year or longer. Unfortunately, one man I was seeing still had a psychotic disorder after 18 months of abstinence. It was a low-grade paranoid delusional disorder with occasional hallucinations. Can imaging help with this?

Chang: I don't know of anyone who has really focused on those patients. It would be very interesting to do imaging studies in the subpopulation of individuals who don't show significant recovery, to see if their brains look different. Either they are predisposed to psychosis, or their damage was more severe.

Imaging and medications

Linde: Many of the methamphetamine abusers we see relapse to escape their withdrawal symptoms, particularly the long-term anhedonia and hypersomnia, fatigue, and low energy. Does the brain of someone who is a chronic methamphetamine abuser look anything like the brain of someone who has depression or atypical depression?

Chang: I haven't imaged the depressed population myself, but, based on the literature, the answer is no. When Nora Volkow, Joanna Fowler, and I imaged methamphetamine abusers, we saw decreased dopamine receptors and transporters and abnormal glucose uptake, concentrated in the orbitofrontal and the parietal regions. Those are not the same abnormalities reported in depressed individuals, which are more in the dorsal frontal areas and usually unilateral on the right side.

Edythe London and colleagues addressed this issue directly in a PET study she published a couple of years ago in the *Archives of General Psychiatry.* She specifically looked at changes in brain metabolism within the first 4 to 7 days of stopping methamphetamine—the period of super acute withdrawal. She found that the more depressed these patients were, the higher the metabolism was in their cingulate area (London et al., 2004). So methamphetamine abusers have brain abnormalities that correlate with their depression, but they aren't the same ones we see in depressed non-drug-abusers.

Linde: The reason I ask is that I take a pragmatic approach with psychopharmacology. I often prescribe antidepressants, particularly bupropion, for the mood component of methamphetamine withdrawal. If people have a history of major depression predating their methamphetamine abuse, that will point us toward using antidepressants more aggressively.

Chang: In those patients, you might expect overlapping brain imaging patterns.

Linde: However, we still go ahead with bupropion sometimes where it is unclear or even unlikely that there is independent depression. What occurred to me reading the article is that there might be support for

this in the imaging studies on dopamine and the pleasure pathway. If dopamine surges are responsible for the drug rush and dopamine is depleted when people become depressed in withdrawal, doesn't that suggest that a dopamine-replenishing medication like bupropion might help? I'm relatively aggressive, too, about prescribing dextroamphetamine or methylphenidate when patients have really severe low energy and anhedonia and literally can't get out of bed.

Chang: How soon after they start treatment are they behaving that way? A long time, or just during the early months?

Linde: Some of them, I would say, through the first 3 months.

Chang: Then do you stop the treatment after that?

Linde: Well, I'm still on the front end of this curve. I've only been doing this for about 6 months. When I talk to patients about it, the vast majority say, "How long do I have to stay on this? I really don't want to be on it long-term." What I've been saying is that once their recovery is more secure, in the range of 6 to 12 months, we will look at tapering them off.

Chang: Are you concerned that they might become dependent on these medications?

Linde: That's a good question. It is a risk. I know I am putting myself out on a limb a little bit in prescribing psychostimulants to these patients. I feel okay about it because the stakes are so high for these individuals. You've got a guy who is a lawyer who has lost pretty much everything. Yes, there is a small risk that he will get a new addiction, but, if he does, it will come from a prescription pad and be legal. He doesn't use needles; he doesn't share needles.

Chang: You're using the same paradigm as treating heroin addicts with methadone.

Linde: Yes. The article made me think I may not be as far out on a limb as I thought. The imaging studies show that a drug's abusability is linked to the rapidity and intensity of the dopamine spike it produces. I'm using oral dextroamphetamine and methylphenidate, which act more slowly and steadily than snorted or injected methamphetamine or cocaine.

I don't do this routinely, but there is a group of patients—professionals, people with advanced degrees, who are not functioning, but have a relatively good prognosis because of their high cognitive baseline and strong motivation to get back to having a regular job. I've seen some actually do that.

Chang: The studies you mention on the role of dopamine in addiction are among the best examples of the power of neuroimaging. Nora Volkow and her colleagues showed that the high a drug produces is proportional to the dopamine spike it causes in the brain's pleasure center, then went on to show that the rapidity of the response also determines the high. Cocaine and methamphetamine, for example, cause extremely rapid and intense dopamine surges in the brain and are addictive. Nicotine, too—in fact, all drugs of abuse.

Those were fundamental insights into why people react to drugs the way they do. The studies also illustrate how learning about mechanisms can help guide treatment. They suggest that the same substitution therapy that uses methadone or buprenorphine to help heroin addicts recover might work for those abusing other drugs too.

Linde: At the same time, from my reading, the findings on substitution therapy for stimulant addiction seem to have been modest so far. I have the impression that the oral dextroamphetamine has provided clearcut benefit only in patients with combined opiate and stimulant addiction who are already enrolled in a methadone program.

Chang: The odds that we will find a substitution that works are good, as imaging is telling us more every day about the neurochemical systems that are involved with drugs. Slow-release methylphenidate is one of the more promising possibilities. It is currently being studied for use in adolescent drug abusers in the Clinical Trials Network. Methylphenidate binds to the same dopamine transporters as stimulants like cocaine and methamphetamine, but it doesn't cause the strong and fast dopamine surge that cocaine or methamphetamine does. It may turn out to be a good treatment, but it would be premature to use it now, because safety studies haven't been done yet.

Linde: I was very interested in the article's mention of GABA enhancers as potential treatment medications. Can you say more about that?

Chang: GABA's role in addiction and GABA-ergic medication strategies are emerging research areas. Dr. Stephen Dewey has been trying to use vigabatrin, or GVG, to enhance GABA function in cocaine and nicotine abusers. This works because GABA modulates release of other neurotransmitters, including dopamine and serotonin. Based on preclinical work with animals and some early clinical work, Dr. Dewey's group thinks it has great promise for treating addictions.

One important potential use of imaging in this area is to measure whether these patients' GABA levels normalize after GABA-ergic treatment. Researchers already have used magnetic resonance spectroscopy to do this in patients with epilepsy. Dr. Ognen Petroff at Yale and colleagues have shown that anticonvulsant treatment with topiramate and other anticonvulsants increases brain GABA levels.

Linde: I've had some success in using a small amount of clonazepam to help patients come down from stimulants. Is it possible that benzodiazepines might do the same beneficial thing that a medication like vigaba-

trin would do—that is, help restore GABA function?

Chang: Wouldn't you worry about their sedative and potential addictive effects?

Linde: I do take those things into account. If a patient abuses a stimulant and also drinks a lot or smokes much marijuana, I won't give him a benzodiazepine. But there is a small group of patients who are strictly stimulant abusers and don't like anything that makes them feel down. There also are some patients, interestingly, whose relapse is triggered by anxiety rather than depression. Maybe they are a subset that has attention deficit hyperactivity disorder. In these groups, I feel relatively safe using clonazepam—even though, ordinarily, the benzodiazepines are the last medications in the world I would want to give someone who already is having problems thinking clearly.

Anyway, when I read what your article said about GABA, I wondered whether clonazepam, for example, may be working on more than just patients' anxiety. Maybe its GABA enhancement has a specific helpful effect on the stimulant-related brain abnormalities.

Chang: That's a good thought. I haven't seen any studies of GABA levels in the brain in stimulant abusers, but they need to be done. We should document whether these levels are abnormal and whether treatment would improve them.

Linde: In any case, you are going to have providers who are open to pushing the envelope a little in the use of medications.

Chang: Right. That's why NIDA is working really hard to test all the different drugs through the Clinical Trials Network.

State of the art

Linde: There is a clinic in our area that uses brain scans along with psychological tests to assess substance abusers and suggest recovery strategies. On a couple of occasions, patients have asked me what I think of this, and I've said, "You can go and get the information, and then shake a little salt on it."

Chang: I get contacted by forensic psychologists who are working on legal cases, asking exactly this kind of question. I tell them that you can't be confident, just looking at results from one individual, that you know how to interpret them. You can't perform imaging in one defendant and conclude that, for example, methamphetamine did or didn't cause him or her to commit murder or a violent act.

So far as drug abuse is concerned, imaging is still strictly a research tool, to learn what drugs do to the brain. The reason has to do with the size of the signal changes that occur. They are relatively subtle. If someone has a stroke or a brain tumor or aneurysm, those are big signal changes that you can see easily, and in those cases we use imaging as we use x-rays, for diagnosis and assessment. Someone who has been using alcohol for many years may develop brain atrophy, loss of brain volume, and you can see the difference with your naked eye. But the kind of atrophy we see with stimulant use—you can't always see it. Instead, you have to measure the volume with very sophisticated computer software. It's the same with the structural and chemical changes. The signal changes associated with drug abuse are so small, in fact, that we have to look at large groups of subjects and average out the results to distinguish those that are significant from the random background noise produced by the machine, differences between individuals, and even single individuals' day-to-day variations.

Linde: The concept that science might pinpoint something abnormal in a person's brain that would directly indicate how to treat it is very appealing, though, for both doctors and patients. For example, "Aha, your amygdala is lacking serotonin. We'll give you x to put it right!"—and x may be a medication that's already on the market for some other indication.

Chang: That is the hope, of course. The machines have improved a lot over the last decade or so because of advances in computer technology and new methods developed by physicists. We're getting more precise measurements, higher sensitivity, better signals. With continued improvement, we may get there. But we're not there yet; at least that's my opinion.

Linde: Your paper mentioned that imaging had implicated genetic variation in transporter activity in vulnerability to drug abuse. Is there a potential for some day using gene therapy with this population?

Chang: I think so. The combination of genes, genetic markers, and imaging can tell us something about who is at risk and who might respond to an addictive drug in a certain way. So, theoretically, that could lead to early targeted interventions or gene therapy.

We say drug abuse is a brain disease. Well, that's right, but it is such a complex disease. Genetic, environmental, and social factors also affect the brain, not only drugs and medications. Imaging may eventually help us sort out those effects as well. &

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