

## **Dr. Nora Volkow Interview**

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## **Dr. Nora Volkow Interview**

Claudia Wasserman:

This is Claudia Wassmann, and today's date is March -- Tuesday, 29<sup>th</sup>. I'm doing an interview with Dr. Nora Volkow.

CW: Yeah, so what I came for is just to -- for the record of the NIH history collection -- to have you tell us about your career, how you got here. If you could start with that.

Nora Volkow: From the imaging perspective specifically?

CW: Yeah.

NV: This is sort of a record for imaging sciences, right?

CW: Yeah, I mean, why don't you start just with something about your personal career and what brought you to the NIH and then we can talk more specifically about your research and the role of brain imaging in this research.

*Male Speaker: I think you might have to go back to medical school.*

NV: Yeah, I know, I did. I started to study the effects of drugs -- I mean, since I was a medical student I was very much interested on drugs of abuse and how you could actually manipulate dramatically the behavior of animals by these drugs.

CW: Why were you so interested in drugs?

NV: Because they have such a powerful grab over controls over behaviors. There's nothing else that can do it so dramatically. So if you want, for example, an animal to work hours in order to be able to get something you

give a drug, an animal will work for hours, thousands of hours in order to get the drugs. So really can't -- I was fascinated by trying to understand what type of stimuli, how is the brain controlled and how these drugs disrupt that regulation. And it's a fundamental interest of mine which is ultimately understanding what makes us make decisions and act. I mean, voluntary actions, I'm very interested on that whole concept of free will and ultimately what is free will. So when someone is addicted to drugs and they compulsively take the drug is that free will? It's not. It's a breaking of free will. So I always like to study situations where the function you're trying to look at is disrupted because that gives you an ability to study the normal brain and the abnormal brain and try to identify which process differs as a mechanism to try to understand.

In fact, one of the -- the other area that I was interested when I was starting my imaging career was on schizophrenia because again I was very much interested on thinking processes and disruption on the control of thinking processes. So again, I was using the paradigm of a schizophrenic that cannot control delusions or hallucinations versus a person that can actually control very much how they, more or less, develop their thinking. So in the case of drug addiction it's a perfect model, and that's how as a medical student as I started to work with -- I was particularly interested in two drugs: one of them cocaine because in animal models it's probably one of the ones that produces the most compulsive administration; and the other one that I was interested were opioids because at that time when I was a medical student this is when they were discovering the endogenous opioid system, [unintelligible] and [unintelligible] at that time, and that was an incredible finding because all of us saw that. I think if I recollect correctly this is probably the first time that they recognized that an endogenous substance that could be abused was actually being produced and have a physiological function. Since then, well, we know that's probably more the rule than the exception -- the same thing, for example, in cannabinoids, you produce your own endogenous cannabinoids that can activate the same things as marijuana. But when the opioids came around this was completely new.

So I started to work on drugs and when I first read that there was this imaging capability that allowed you to look into the brain I said, "Wow, this is an extraordinary opportunity to start to look at the effects of drugs in the human brain." So I started -- the reason why I actually did my residency training -- I was born in Mexico so I went to medical school in Mexico where I was doing research on the effects of drugs in primates,

actually and rodents. Then I came to the United States to do my residency in psychiatry, I chose New York University because it was associated with Brookhaven National Laboratory, which at that time had the first PET scanner that was functioning and they had synthesized these molecules that allow you -- there was a sugar that was labeled with a positron emitter that allowed you to monitor how the brain uses sugar -- sort of opening the possibility for the first time look in the human brain, noninvasively -- how active the brain is. Why? Because sugar is picked up under normal physiological conditions as a function of brain activity.

So I came to New York for that and I started to work, and I was -- my first project on imaging, actually, was not on drugs, it was in schizophrenia; again, on the same line of thinking, on trying to understand, again, a model where your brain is disrupted here in terms of cognitive process might merely disrupted. From there I went to study the effects of cocaine. So I started with schizophrenia and then I started to work with the effects of cocaine and the effects of alcohol.

At that time, of course, it was very, very early in the whole imaging field. There was no data, there was no work on substances of abuse and so I started first with cocaine because I had been interested when I was a medical student. I have done work with it. I found out that the brains of cocaine abusers looked like they had strokes, and this was the beginning of the '80s when cocaine was very popular, where the general belief was that cocaine was very safe and here were these findings. And I remember, also, we were doing extensive neuropsychological, classical neuropsychological testing, on these patients and they were normal and yet their brains looked like they had vascular pathology.

So I submitted a grant to NIDA [laughs], which was rejected on the basis that there was no evidence that cocaine was disruptive or toxic as evidenced by the fact that my patients have perfectly normal neuropsychological tests. I still have the pictures of that. [unintelligible] there must be some place. [laughs] I always tell this story when I get [a] young scientist that get all discouraged that their grants were rejected and I say when you come with very unexpected findings you will always get the reaction, "I do not believe this." So it's a normal event of things. Humans have a certain background and context of knowledge with which they judge so at that time this was a big surprise, nobody believed that cocaine was toxic. Then what helped me -- so I had submitted, also, a paper to the *New England Journal of Medicine* that rejected it. There was no evidence

of cocaine being toxic, though there was evidence the amphetamine was toxic, and there had been a couple of papers reporting many years ago that it was producing arthritis, it was producing vascular pathology from inflammation. But that was amphetamine, and amphetamine for many years has been recognized a much more dangerous drug than cocaine. So what helped me in terms to get my paper published and getting the grant accepted was finally that unfortunately two major athletes died from minor doses of cocaine, which alerted the medical community that cocaine was not such a safe drug.

CW: So can you say what year was this? When was this?

NV: When did he die, '86/'87?

*Male Speaker: Len Bias was in the '80s.*

NV: '80s.

CW: So your first grant application to the NIH was in 19...?

NV: The beginning of the '80s, it was just before these individuals died. It must have been '85/'86.

*Male Speaker: Yeah, it must have been about '85/'86/'87.*

NV: Yeah, it was exactly -- I had just gone to Brookhaven.

*Male Speaker: '86, '86 I think.*

CW: At that time did you have a scientific mentor? Was someone particularly important for you?

NV: No, I didn't have a scientific mentor. I actually, when I was -- when I was in medical school, yes, I had a pharmacologist Julian Villerreal, who was an expert on opioids and who had done his graduate work and postgraduate at the Michigan University, which at that time was one of the main centers for drug abuse research. So he was my mentor when I was a medical student doing research, but once I left and I came to New York University I was very much on my own. And then when I went to Texas I also was very much on my own because there was no one doing that work. So it is -- I was in an imaging center that was directed by cardiologists. So

very much throughout my professional career -- because I've gone into new territories there has never been anyone -- except when I was a medical student it was very good for me to have Villarreal. I haven't [?].

And so then I started to work with cocaine. It became clear that cocaine-- because clinical reports started to be published of these patient becoming paralyzed when they were taking cocaine-- and the paralysis of course were varied. It could be very mild, like a mild facial paralysis that only the patient would pick up or it could be an arm. But there were severe paralysis, and what happens is cocaine is vasoconstricting and so by producing vasoconstriction and by increasing blood pressure it can lead to hemorrhage or a stroke. That was then recognized and there were many papers published after that evidenced that cocaine was producing cerebral blood flow defects.

So at that time I was no longer interested. I don't like to replicate what other people are doing. In a sense actually it's one of my -- I guess prejudices in life. I guess I like to go for new territories. So I started to work and I also in a more fundamental level what I was always intrigued was the element that was leading to the loss of control. That's ultimately what I've always been fascinated about drugs and addiction. So I started to go into that. What happens in the brain of a person that's addicted to drugs? And so I started to use -- the two drugs that I started to work initially with, cocaine and alcohol. Throughout my career I've maintained work on those two drugs. So since 1985 I've been working on these two drugs. In the process of course I started to work with other drugs, heroine, marijuana, nicotine and more recently methamphetamine, but -- and my strategy is to actually take two drugs and study them in parallel and see what commonalities they have and what are the differences. I like the concept of same commonalities because if you look at the process of addiction -- whether it is nicotine, whether it is methamphetamine, whether it's cocaine -- the compulsive administration of the drug is ultimately the same basic phenomenological characteristic and the same thing with alcoholism. So trying to identify that what is common that leads to the compulsive drive and inability to stop the intense urges to take the drug, and then of course understand how each drug does it separately.

So that's when I was -- that's when I met Dr. Fazil and actually I was very interested. There was animal data showing the drugs of abuse, all of them increase dopamine and that actually activates the reward circuitry of the brain and that's why drugs of abuse could produce addiction through this

mechanism, the dopaminergic mechanism. But what was not understood is they knew the reason why an animal will self administer these drugs was in part related to the fact that all of these drugs increase dopamine, what was not understood is what is addiction, because if you take an animal that's not addicted and you give them the same drug, dopamine goes up in their brain whether they are addicted or not addicted. So that's not at all the pertinent variable because you otherwise wouldn't see a difference between them. So I started to ask that question, is the dopamine system at all involved in the process of addiction and if it is how does it get -- I mean what is its involvement? So I started to study the brain dopamine system systematically and that's what I've been doing with increasing more complex questions. Is it disrupted drug addicted people? We found that, yes, indeed it's disrupted.

Others since then have also found that and what appears to be ongoing, and we don't know if it's the effects of chronic repetitive use of drugs or whether these individuals to start with had an abnormally functioning dopaminergic system that made them at higher risk. We don't know if it's one or the other-- whether this is chronic use of drugs or there was an elemental fit that made them more vulnerable. But we have, and others have, documented is that addictive people clearly documented for -- clearly, clearly documented for cocaine which has been the drug addiction that has been studied the most, have decreased functioning of dopaminergic pathways. How is that so? Well the decrease function of the dopaminergic pathways is evidenced when the subjects are tested without taking the drugs. So if you take a person that's addictive and you study them one week after cocaine or three weeks after cocaine, or three months after cocaine you see that the receptors that are postsynaptic transmitting dopamine signals for once are down regulated but you also see that the amount of dopamine that has been released by dopamine cells -- which is the main way that the dopaminergic system transmits signals -- is markedly blunted. So you see a reduction that comes from the dopamine cells signaling but also a reduction that will occur from down regulation of the receptors, which are then going to transmit that message.

Now we -- that abnormality, decreases in receptors and has been documented not just for cocaine, it actually has been documented for other types of drug addictions including alcoholism. We reported on alcoholism and we reported on heroine and methamphetamine reductions in the two receptors. We have not -- with respect to dopamine release, that has been documented in cocaine and the group at Columbia University has also

documented it in alcohol. We've been studying alcoholics and the magnitude of that disruption is not as large as you see with cocaine. So even though the group at Columbia has clearly showed an effect that work is marginal. So what then was, okay, we're seeing that decreases in dopamine function in cocaine addiction, how does that at all help you understand the process of addiction? How does -- if it is involved how is it disrupted? And for once you can go from the theoretical perspective and say well-- what do you know about the dopamine system that such an abnormality will help you conceptualize that there is a problem?

The dopamine system is a neurotransmitter that's involved with multiple functions, but for us there is a function that has been associated dopamine that initially was equated with reward. So people would say, "Well the dopamine system is translating signals of reward." However, over the past few years it has become evident that the dopamine system is not just about reward. It's about something that's much more fundamental and primary than reward, and that's saliency. So when the individual is faced with something that is salient and salient would be any stimuli that pertains to the well being and survival of that organism and that is the way that nature insures that you will pay -- you will give priority of stimuli that are really indispensable for survival or for stimuli that you need to pay attention because if not they can actually kill you.

So which are things that are salient? Reward is salient. It so happens, that nature has made us do things that are important for survival by associating them with pleasurable responses. So food clearly can be very pleasurable. Sex can be very pleasurable. Social interactions can be very pleasurable, and that's the mechanisms by which nature insures that you seek--for example-- groups of people, that you seek -- actually it has even been even shown in humans with imaging technologies that beautiful faces activate the dopaminergic system. So this process by which you are molding your behavior in one way through reward, pleasurable responses that are going to activate dopamine, but you are also activating dopamine by aversive stimuli.

So if, for example, an animal is placed in a cage where there's going to be an electrical shock if you place that animal again dopamine cells will fire. Why? Because if you don't pay attention -- it's the way by activating dopamine cells you're actually driving your priorities to pay attention to that, to engage your activities to that. And so if something is dangerous and you don't -- are not able to engage your activities like that, guess what



happens. You don't pay attention and that will have seriously detrimental consequences. So say for example an animal eats poisoned food. That activates dopamine cells, and dopamine cells the only thing that that they do by being activated is not only engaging your -- the brain to pay attention to the task they also facilitate memory and that's a different type of memory. It's a memory that's associated with emotional responses. That we call conditioned. Where you have a memory that's associated either with a pleasurable or an aversive effect you will have -- you will be much more likely not to forget it, number one, but also when you are exposed to it again, to recreate it. Not recreate just in the way that says, "Oh I remember  $2 + 2 = 4$ " but to recreate the sensation, which of course is much more powerful because that modifies your whole motivational inner state. That's in a different area of the brain than classical memory, which is hippocampus, this amygdala.

Now, memories in the amygdala are very powerful in driving your behaviors. Why? Because they condition you. So they condition you -- so that experience to me of eating an apple and getting mortally sick -- next time I see an apple I may feel nauseated, that's a conditioned memory. But that's perfect because it will avoid me to put myself at risk. The same thing if I eat a chocolate and it's extraordinarily delicious, next time I see the chocolate, I'm going to salivate. And I'm going to want that chocolate, even whether I'm hungry or not hungry. Well, what drugs are doing, that's exactly one of the aspects of why it's so powerful. By activating dopamine in the brain, they're telling the brain, "This is very salient," they are creating a very powerful conditioned response, such because that's a nature machinery of the brain, to actually, when something is very rewarding or something is very aversive, to condition you to either avoid it or to approach it, and to give priority because this is actually salient.

So what happens there is, of course, drugs will enhance conditioning, and a person that is addicted and has decreased dopaminergic function, let's call compact, how do we theoretically conceptualize it? Well, the obvious one is this first one, will have decreased sensitivity to natural reinforcers, the natural -- the events that should be salient. And we pick it up always on the positive side, is this okay? And, indeed, people, I mean scientists, have documented that, that individuals that are addicted to drugs, heroine abusers, cocaine abusers, even nicotine addicted people, are less sensitive to natural reinforcers. And for example, in the case of cocaine addicted individuals, they have been shown, using imaging, that their brain

circuitries limbic areas respond much less to an erotic video than their normal counterparts that are not addicted. Exposure to food also activates much less reward circuitry in people that are addicted. And so, what is the consequence of that? So if you're addicted to a drug, what's going to happen? And you have decreased dopaminergic function, you are going to be much less responsive to stimuli that are normally motivating our behaviors. And I put food and sex, but as I say, it also pertains to much more complex behaviors than that, like social interactions, like the reinforcement that wants you to write a paper, or the drive that makes us want to learn.

But the other thing that really very few people have thought about, that is this also as important, which has made it extremely difficult to understand the behavior of the person that's addicted. You have decreased dopaminergic function, it's going to be making you less sensitive to natural reinforcers, but it's also going to be making you less sensitive to aversive negative reinforcers. And there's the notion that people, says, "Well, how come a cocaine addict could actually take the drug even though they knew that they were going to be placed in jail?" Well, the system that sends the signal of "This is salient, pay attention to it" -- whether it's positive or you should avoid it, is not working properly. So that sensing, filtering process is disrupted. So that, for example, could underlie the disruption in behavior that makes an individual, first of all, much less sensitive and much more apathetic and indifferent to natural things that would otherwise motivate our behaviors. But also, much more indifferent to normal punishments that we would say, "I will never do it. I mean, I don't know how anybody can basically risk those consequences."

The other element about it is that the person that's addicted to the drug, again, you learn, you learn from, basically, experiences. So they are learning, like if I see something that's very reinforcing, I listen to a piece of music and I said, "This is extraordinary," it's very reinforcing and I learn about it, it motivates me so next time I go and buy more CDs and I listen to it. But the person that's addicted to a drug, if they have less sensitivity to these reinforcers, they learn it. They learn that these reinforcers are no longer able to motivate their behavior. Now what happens when you are not motivated by anything? I mean we all -- you get very bored, and it's a very, very stressful situation. Boredom in itself is something that we have not studied, but in fact is something that it would be -- I don't know why anybody has not done yet an fMRI [Functional Magnetic Resonance] study on the state of boredom. But we

should probably speak with [unintelligible] to do something like that.  
[laughter]

How does the brain look when you're bored to death? And on -- also one of the questions that I've been asking myself, is how is the concept of -- what is the function of boredom? I mean, as I say, nobody has paid attention to it, but it's a universal phenomenon. Theoretically I have no data to show this, but again we can think, I mean we all felt boredom. To me, it's likely that it has a function just as thirst has a function. And through boredom is a mechanism by which nature ensures that we actually engage in an activity that will get us out of that state, just like thirst engages you into getting water such that you get out of that state, the process of boredom engages you to get out of that state. So it's a very natural process, so the drug-addicted person has learned -- I mean, and I always say these jokingly because people -- I don't know why it always makes people laugh because it's the truth, that I go and look at data. I love to look at data, I mean there's nothing that makes me high more than data, particularly if the data behaves properly and is interesting. But every person does different things. But if the person that's addicted, and they know that data will not do it of course --[laughter]-- they may go ahead, and they know that the drug will. Why? Because the drugs, even though they have decreased dopamine function, decreased receptors, drugs activate the dopaminergic systems in a much more potent way, and for much longer periods of time. So they actually can compensate for that deficit. And so they take the drug, and that makes them more vulnerable. So that's, I think, one of the mechanisms by which individuals, which either because of chronic use of drugs or because of specific developmental changes that happen like exposures or genetics, have a disruptive dopaminergic function leading them to be less responsive, and the dopaminergic systems being less responsive, maybe at higher vulnerability to take in drugs because of these mechanisms I've been discussing.

But also in parallel, we've taken another avenue and sort of said, you can, at the same time that we've been measuring dopamine function in these individuals, we've been measuring how their brain functions. We do that by tagging glucose, by seeing how active the brain is, and identifying if there are areas of the brain where when there are decreases in receptors translating to disruption in activity. And what we found, which was absolutely unexpected, is one of those situations where the data completely takes you by surprise. There is no hypothesis; I mean, it's one

of those things that says, "Wow." It's that it's the frontal cortex, and the frontal cortex when we first found it, and it was many years ago, in 1987, '88, again, nobody paid attention, there was one paper in *Animals* documenting that drugs could affect the frontal cortex. But that was it, I mean tens, hundreds of papers and what we were seeing is that the disruption in the dopamine system was associated with abnormal activity in very specific areas of the frontal cortex. The frontal cortex is very large in humans, and their subventral part, that is the lower part that is highly connective with limbic areas of the brain, very much involved with motivation and evaluation of stimuli as a function of context, very dynamic, very complex.

Then you have the classical, more -- deeper areas, but also ventral, regulating attention and also involved with your ability to inhibit. So if you are faced with two situations and you want to actually choose one but you say, "No, it's not a good idea, I should choose this one." That operation of being able to inhibit one response that you may have a tendency to favor, but cognitively suppress this part of the frontal cortex.

You also have involvement of the areas involved with executive function. And executive function ultimately is the ability of the frontal cortex to carry on multiple operations, that's why it allows you to carry on multiple operations at the same time. So in an elemental way, we always are doing that. You are carrying in a conversation, you are carrying the logic of the different things that you are doing in terms of actually to also in your brain or in my brain, what I'm carrying that information in order to make a point. Well, at the same time being very much aware about the time and that I need to take a plane and things like that, so we all can multi-task in many ways. Ultimately that is possible because of the abilities that you have in the frontal cortex.

Well, those areas where abnormal -- where the decreases in dopamine were occurring were also associated with disruption in these frontal cortical areas. And as I say, it was a surprising finding because it documented that perhaps the process of addiction, the involvement of the dopamine system in addiction was by disregulating these frontal cortical areas, which was very different from the traditional way of sort of saying, "Oh, it's the limbic brain, the amygdala, the fame of the amygdala." Here we were documenting frontal cortex. Now, and it included frontal cortex that is intimately connected with limbic brain, but it included frontal cortex that is not intricately involved with a limbic cortex -- more higher

cognitive functions. I've focused more of my work on understanding the implications of that frontal cortex that's links with limbic areas of the brain because that's the one where the differences are the greatest between addicted people and non-addicted people.

And so, what we have shown and others have also shown is that when you expose drug addicted individuals to stimuli, for example, that are drug related, to activate these areas of the brain that are very hypoactive when the person is not exposed to drug stimuli. These areas of the brain, as I said, when I found them abnormally in addicted people, there was nothing I really knew about them except that they were disrupted in patients that had obsessive compulsive disorder, and that was sort of a very interesting finding. In fact, that probably to me was one of the -- that finding gave me a completely different perspective on the process of addiction because I jumped on it and I said, "Well, it's not -- what do these two diseases have in common? I was sort of saying, "Well, the imaging is showing that the similar circuit abnormal in patients with obsessive compulsive disorder and in addiction," and then of course it jumps at me that a basic core of the phenomenology in drug addiction is that compulsive administration of the drug.

And so you can look at the person that has obsessive compulsive disorder and they will -- and it's hard to understand, and they'll say, "Doc, I just -- I mean, I wash my hands, and I wash my hands. Of course I know they are clean, but I have to continue washing them because if I don't wash them, I feel very anxious and ultimately I cannot cope." I mean, they are inclined to inhibit it, they are trying to inhibit not washing their hands, but it overcomes them. And the addict tells you the same thing, "I don't want to take that drug anymore, but I just cannot stop it." It is actually -- and I've seen patients that have said, "The moment I left the hospital, I did not want to take the drug, and without even realizing it, I already have the drug in my mouth," or smoke or whatever they take. So that compulsive drive in many ways is similar, what leads to that state, of course, is likely to be very different.

But once you have disruption of these areas that actually play a role because you have to realize that the brain optimizes its resources, so things -- you tend to go into automatic and habits and sort of you create these responses. So it's likely that part of the problem with drug addiction involves disruption of these areas of the brain that allows you, once you identify something as salient, like when you're sitting in front of the food.

You'll eat it up. Initially you'll taste it, I mean it tastes good, but most of the meals go in an automatic fashion. Of course, what happens when -- what makes you stop, there's no more food or someone distracts you or you feel full. But if you disrupt the orbital frontal cortex, these animals, if they are animals, will continue to eat and eat and eat and eat and eat and eat. And they will, for example, if you put them -- they persevere the behavior, they repeat and repeat and repeat and repeat and repeat.

So if you have an animal that you train them to press a lever, and then as an investigator you remove the food. Because you make them press a lever if there's food, but if there's no food, they say, "Why should I press the lever," right? Well if you damaged your orbital frontal cortex, the animal learns to press the lever for food, but if you remove the food, the animal continues to press the lever again and again and again, even though it's not rewarding anymore. And it's hard to conceptualize, and you sort of say, "Well, what's going wrong?" I mean, imagine that that was a person that, the rat doing that and doing something that basically has no sense, no longer any sense. The ability to change your behavior as a function of changing characteristics of the environment is in part driven by the orbital frontal cortex. So the animal has lost the ability to recognize that the environment has changed and that's no longer reinforcing and continues to do it and do it and do it. So that sort of, in my brain, uncovering, and again, imaging made me realize that this is an aspect about why dopaminergic pathways may be promoting the process of addiction -- is by disrupting these frontal cortical areas.

And the last paper -- which is actually in press now -- that we had, which had been a study that I had been wanting to do for many, many years, very difficult to do, but we finally got it out, is that -- again, you sort of say, "Oh well, drug addicted people are less sensitive to monetary reward, they are less sensitive to erotic stimuli, they are less sensitive to food stimuli." But ultimately what I have always been intrigued about is what if you were to give them the drug, how would they respond differently from a normal person versus an addicted person? Now you cannot give cocaine to a person that's not addicted because that's unethical, but what you can do is select [a] pharmacological agent that may share the reinforcing rewarding pleasurable responses that cocaine has that's actually a therapeutic agent, and you can do that, and that's that strategy we have been using. So we've used that drug that we use for the treatment of attention deficit disorder, methylphenidate Ritalin, and when you inject it intravenously into cocaine abusers, they report that its effects are very

similar to a dose of cocaine. The issue though is that it is a drug that has different pharmacokinetics, and a pharmacokinetic is its temporal course of action, which do not favor the repetitive administration that you see with cocaine. So, and that's why it's not a drug that is abused like cocaine.

So we tested and compared the responses to intravenous methylphenidate between people that are addicted to cocaine and people who are not addicted to cocaine. These individuals have had experience in the past with stimulants, they are not addictive they don't fill criteria for abuse. So they have been occasional users. These people are clearly addicted. And you give them intravenous methylphenidate and you see what happens. Cocaine abusers like it very much -- very, very much. They say it's very similar to cocaine; it increases dopamine. Interestingly, the magnitude of the increases in dopamine much less than what you see in controls, that by the way, don't actually -- some of them like it, but some do not like it. So it's not a consistent response, so it's not dopamine, and that's what I was saying, it's not that what's going to distinguish the addict versus the non-addict is not that the drug is posing more dopamine. It's actually, ultimately, and that's what we're publishing now, is the activation of the orbital frontal cortex only in the addicted people. Only in the addicted people does intravenous methylphenidate activate the orbital frontal cortex, and that activation is associated with a desire to take the drug.

So this brings us back to the concept that very much adaptations in these area of the brain that make it, that is the one that actually whose function is to, among other things, to put that value of our reinforcer and the value of our reinforcer is something dynamic. Because say, for example, that you had a chocolate chip cookie now, it would be much more reinforcing now than if you had had five of them. So after five of them, it loses any value whatsoever. So that's exactly why reinforcers are a function of its context. That area, the orbital frontal cortex -- that puts value to all of the stimuli that allows us to motivate and change our behavior as a function of the context. That is abnormally disrupted in addicted people, and it is hyperactivated by the drug stimuli in a way that is qualitatively different from what you see in a control.

Based on these imaging studies, what I -- what has -- basically these findings led me to conceptualize, is that dopamine is indeed involved in the process of drug addiction, that in both, in the initial motivation to take the drug producing the conditioned responses, but also by producing

adaptations in frontal cortical areas that are then going to motivate the behavior to give it priority over everything else.

Now, it is also evident that while the dopamine system is involved, it is also clearly evident that there are other neural transmitters that are involved in these adaptations. There are two that have generated major interest, glutaminergic ones, and there is some very elegant work that has been done mostly in animals because we cannot test these yet in humans, we don't have the tools for imaging. Showing that there is an enhanced sensitivity of the cortical pathway that regulates the cortex, the frontal cortex, regulates dopamine cell firing and dopamine release. And so when we're seeing these abnormalities in the humans in the frontal cortex, it's likely that they in part reflect these adaptations in the glutaminergic system but then feed back into the dopamine system, which is the one that ultimately motivates your behavior, through either the pathways that are signaling this is salient because it's reinforcing, or this is avoided because it is something that is non-desirable.

CW: Okay. Well maybe we should take advantage of the fact that we are four -- that we have three more scientists sitting here so that you could maybe say something about where you want to take, what are your objectives for the NIDA and what kind of imaging studies do you do or do you envision?

NV: Okay, in terms of the drug addiction there are many, many -- I mean, a wide variety extremely important potential imaging studies. Elemental number one, understand better the functioning of the developing human brain and there is a large multiple institute project right now to evaluate changes in brain morphology that occur from early age until late adolescence. That's -- so to actually delineate how the brain changes and how the tissue composition of the brain changes and how it gets connected. In parallel it would also be extremely important to understand how those morphological and connectivity changes are going to be affecting the function of the brain. So while there is this large inter-NIH project on -- focused mostly on tissue composition and brain morphology we need to develop the next one which will target the same way in, a very systematic way, the understanding and how that effects brain function, which also is going to require brain imaging.



There is the other element in terms which is much harder to do but one could do it certainly -- start to evaluate it in a more careful way at the beginning until we get more sensitive tools in primates, nonhuman primates, which is to look at receptors and neurotransmitter systems as a function of aging. Like what we were saying is that the brain dopamine system is very important in drug addiction and so is the glutaminergic systems. Well, how do they differ as a function of the stages of development that you are in? And why do you want to study that for the field of drug addiction is that drug addiction starts in adolescence and so if you haven't become addicted to a drug by age 21 and for some by age 25, the probability of getting addicted is not zero, but it's very, very low. So the question is what is unique about the brain of an adolescent that makes it particularly vulnerable, number one, to seeking the use of drugs, but number two, to addictive process. The epidemiological data for example is showing that the earlier you start a drug the higher the risk that you are going to become addicted later on in life. So there is an element that we don't understand well about what we know that vulnerability during that stage of development is very, very relevant but we don't understand the neurobiological processes that underline -- that's one of them.

Then we're also -- there's another area in terms of where imaging is likely to be playing an important role and that has to do with understanding the effects of the environment. So for example, we know that a stress is one of the variables that facilitates the acquisition of drug self administration in animal models. We also know that stress basically promotes relapse in people that are addicted to drugs at different stages during their detoxification. And we -- so we know that in humans, from epidemiological studies again, one of the variables that is considered a risk factor for taking drugs is stress. So neurobiologically what is -- why is that? Why is it that stress makes an individual more vulnerable to taking drugs or to relapse? Well, you can start to use imaging to investigate what are the neurochemical consequences of these stressors?

We can use imaging to also start to look at the interactions -- an important aspect throughout the whole medical field is the realization that genes play very important roles in a wide variety of diseases. Now what has also become clear -- particularly more evident in complex diseases but even in non-complex ones -- is that genes by themselves, while they account for a certain percentage of disease process, the burden of genes by themselves, pristine genes by themselves actually is very small. It's the gene interacting with the environment that's producing the disease, and that's

relevant for things like cancer. That's relevant for things like asthma. That's relevant for things like obesity. That's relevant for mental illness. That's relevant for drug addiction. Now why is that so? In the case, for example, of depression there was that elegant study shown that there is a gene that has been associated with a high vulnerability for depression, but what these investigators found was the gene by itself was not guaranteeing that you were going to get depression. You will get depression if you have the gene but you were exposed to certain stressors during your life. And the same is very likely to happen with a process of drug addiction. So when we speak about the concept of heritability in drug addiction for example, it is estimated that approximately 50% of the vulnerability for drug addiction is genetically determined. Except when you look 50%, that 50% is going to vary depending on whether you make the measures. So if you go to a place where they are absolutely no drugs -- you go to Utah, I guess. There are very few drugs in Utah. You will find out that the genetic is very tiny because there is no one there taking drugs, right? So it is again the interaction of the gene with the environment. So when you are speaking 50% vulnerability that will, the genetics by themselves and the genetic with the environment component. So it's not a simple 50 environment, 50 genes; they interact in very complex ways. Clearly for a wide variety of diseases that appears to be the case, and certainly the ones related to -- that we call complex diseases -- it's like to -- -- the serotonin transporter and individuals using imaging have started to look at it when they get exposed to stimuli that are stressful and you look at imaging and the responses of imaging people. So if someone had the allele that makes you vulnerable to depression and you get exposed to a stressful stimuli, how does your brain activated itself that is different from that of someone that does not have that gene?

As we start to uncover, for example, the genes that are likely to be involved with drug of addiction we can start to do exactly the same consequences because stress is one of the variables that determines -- makes you more vulnerable to taking drugs -- we would have to start to sort those genes. For example, we could start to look at the same type of questions. Maybe that gene makes you vulnerable -- how do you respond to stress or how do you respond to a natural re-enforcer? You can start to understand how the genes are modulating the function of your brain that will then help you understand why they may be involved with drug addiction. So that's an extremely important area of research that we are going to likely be seeing into the future. Another -- I mean, there is a whole list of things that one can do with imaging. One of the ones that we

have been speaking a lot among ourselves is in treatment development, so in behavioral interventions. One of the things that, for example, I've always challenged people -- so that I hope someone starts to do these studies. I know that there is a grant. I know one of my colleagues is putting in a grant on this. It's very important in relation -- we don't have it, but we have identified areas of the brain that are dysfunctional in people that are drug addicted, like the orbital frontal cortex, the inferior cingulate gyrus, the ventral anterior cingulate gyrus. So the parts of the prefrontal, executive function-- Can you exercise those areas of the brain to strengthen them, just like what you do with kids that cannot properly read? That they've shown with imaging that in those kids that have dyslexia, that can actually not read properly, the areas of the brain that are normally involved with reading don't get activated. But as they start to exercise them they see compensation and they start to improve actually in their reading skills.

So the concept is can we use imaging to help us design interventions that can strengthen those areas that are abnormal? This, for example, has also been used elegantly in patients with stroke where you see the defect, and so you start to exercise the area of the brain that actually -- that is no longer able -- you put them to do exercise of that function that is impaired, and you start to see how other areas of the brain take over and start to do it. So you're guiding yourself on interventions through imaging technologies, the same thing with medication. One of the aspects that's very eloquent in terms of medications, we can start to ask questions -- those, for example, can we start to think about medications that strengthen that same [unintelligible]? Like let's not just think about the medication that we're going to block this receptor. Start to think about can we strengthen the operation of this area of the brain and can we use imaging the other -- there was an elegant paper just published in the *Archives of General Psychiatry* showing you can actually use medication to actually help you learn something that can be therapeutically beneficial. So this was done in patients that have panic to actually go into closed rooms. So they've shown that if they gave them psychotherapy to actually desensitize them under those conditions with medications they actually -- those individuals were much better able to learn the paradigm and they had much better responses in terms of their anxiety reactions, so that the combinations--so it will be real -- it would be fascinating to do in parallel the imaging studies to start to understand how that's happening.

So these are just -- I mean, I can go on and on and on and on, but I think that I will overwhelm you with examples in terms of how we can use imaging.

CW: Okay. Thank you very much.

NV: You're welcome.