Brain and Mind  
May 13, 2004  

Nora D. Volkow, MD  
Drug Addiction: The Brain in Disarray

Introduction by Richard Mayeux

Richard Mayeux: For those of you who have persisted through this afternoon, [you] are in for what I think, what's going to be a very exciting talk. Reading through the papers by our next speaker have just sort of illustrated to me the very usefulness of brain imaging in understanding the basic disarray in the brain for disorders of substance abuse and addiction.

Nora Volkow is the director of the National Institute on Drug Abuse, or NIDA. Prior to that she was at the Brookhaven National Laboratory as the director of Nuclear Medicine, and the director of the NIDA Department of Energy and Regional Neuroimaging Center there. She was also a professor in the Department of Psychiatry and the associate dean for the medical school at the State University in Stony Brook.

Her research investigates the mechanisms underlying the reinforcing addictive and toxic properties of drugs of abuse in the human brain. She was the first to use imaging to investigate the neurochemical changes that occur in the human brain during drug addiction. And most recent studies have employed imaging to investigate the effects of stimulant drugs and to examine changes that occur with aging in the dopamine system. She's a recent member of the Institute of Medicine, and was named the Innovator of the Year in 2000. I'm pleased to introduced Nora Volkow, who's going to talk on drug addiction and the brain in disarray.

Neurobiology and Drug Addiction

Nora Volkow: Good afternoon. It's a pleasure to be here, and I want to thank the organizers for having included me in this wonderful symposium.

I'm going to be changing subjects, and this is the brain in disarray, which I call the state of drug addiction, which is actually . . . what intrigued me about it to start investigating drug addiction, which I started 25 years ago, was the notion that in people that are addicted, one of the characteristics that we value the most as humans—that is our ability to choose, to do our behavior and be able to carry it,
our ability to control our behavior—is markedly disrupted. The person that's addicted to drugs does not choose to be addicted, and what happens is at the time that they end up coming to see a psychiatric unit they basically are at the point that they realize that they no longer can control their behavior and they need our help. So it was this paradigm that actually led us to try to understand what happens in the brain of an individual that, even though they consciously want to stop taking a drug, they are no longer able to do that, or it's very difficult for them to do that.

Drug addiction is a disease of the brain for which we have a culprit; we have drugs, we can point a finger at drugs. However, we also realized that the chronic drug exposure, while in some instances leads to addiction, in others it does not, and what has become evident is that there are other variables that are indispensable and necessary for the addiction to occur. A very important one are those biological and of them, genetics have been identified by studies in humans. It has been shown that close to 40 to 50 percent of the disease of addiction is indeed accounted for by genetics. There have been multiple genetic studies, there have been several loci in chromosomes identified and replicated, but there's no gene yet that has been linked directly to drug addiction, except for specific ones that relate to metabolism of drugs such as nicotine and alcohol. But for the most part we do not have the genes that can be linked to the genetic predisposition for addiction.

It is also evident that environment plays an extremely important role, and here I have to be careful because of the previous speaker. And when I speak of environment the variables that come forward as some of the most relevant ones in enabling addiction are those that related to stress, acute as well as chronic stress, and of the stressors that are linked with addiction one of the ones that are stronger are those related to social type[s] of stressors.

So in this paradigm how do you try to understand what are the neurobiological changes that lead to the phenotype of drug addiction. And before I go into that let me make some disclaimers at the beginning rather than at the end. When you are doing studies where you do not know the genetics it becomes harder to target a particular system, number one. Number two, in a process that you’re studying drug addiction what happens is you get the individuals when they are already addicted so you do not know the extent to which the changes you are identifying were there before the person became addicted, or whether in fact they are the effects of chronic exposure to drugs with interactions of the other variables. Also the other disclaimer is if you go into the brain, which system do you go into? And we chose to specifically investigate the brain dopamine system, and I made it very clear here, not because we believe that drug addiction is just involving the brain dopamine system, because we wanted to identify what the role of the brain dopamine system was in the process of addiction.
The Dopamine System in Addicts

And why did we choose that in that case, dopamine as a neurotransmitter to go after? It was because there's multiple studies that have been done in laboratory animals showing that basically all of the drugs of abuse that can produce addiction in humans, all of them increase dopamine in the nucleus accumbens. And this ability of drugs to increase dopamine in the nucleus accumbens has been shown to be extremely important in the reinforcing effects of drugs of abuse. So drugs, when they are taken, increase dopamine in the nucleus accumbens and then that is linked to what we have been calling reinforcing.

For many years it was traditionally felt that reinforcement, that is the characteristics that will lead the animal to take it again and again, was equated with pleasure, and many studies for many years equated dopamine with pleasure. For the past ten years of neuroscience research, it has become clear that the dopamine system which is targeted by drugs is not per se relevant, perhaps to hedonic pleasure, as we call it, but actually signals something that is more indispensable for survival and motivation, and that it signals the saliency of a particular stimulant. And pleasure is one of the characteristics that make the stimulus salient. But by the same token an aversive stimulant can also be salient, a novel stimulant can also be salient, an unexpected stimulant can also be salient. And so what it is basically telling us is that drugs of abuse are activating the system that is the way that the brain will process something as salient.

Now one of the aspects that has been said is yes, it is recognized that the ability of drugs to increase dopamine is indispensable for the reinforcing effects, but how does that explain the process of addiction? And it doesn't explain it, because if you were to give a drug—and this has been done in animals and humans that are not addicted to the drug—and compare the response to that of an animal or a person that's addicted, what you find is that the drug is able to increase dopamine in the nucleus accumbens in both the addicted and the nonaddicted subject. In fact, in certain instances the response is even larger in the nonaddicted person. So that ability of the drug to increase dopamine per se is definitely not giving us any clues about what is it that leads the person to lose control and engage in that compulsive pattern of drug administration that characterizes drug addiction. So we decided to do the studies and ask the question, Is the brain dopamine system at all involved in the process of addiction, and if it is involved, how does it help us understand the phenotype?

PET Studies of Addict Brains

So we used positron emission tomography to investigate different molecular elements involved in dopamine neurotransmission. And at the same time we used a strategy—this has been going on for the past twenty years—of investigating a wide variety of addictive disorders. So we started alcoholics, we started cocaine abusers, we started methamphetamine, heroin, marijuana . . . and what we've
been interested by studying and comparing all these addictive disorders is to identify if there are common abnormalities of all those diseases, of all of these addictive diseases. And the reason why is we are not per se interested in understanding the specifics that relate to cocaine addiction versus alcohol addiction, but to understand the common characteristics, the common neurobiological processes, that explain the common phenotype, which is this one that is the same in an alcoholic as in a cocaine abuser, which is that inability to control the intake of the drug, even though they consciously don't want to do it, and the engagement of this compulsive behavior of taking the drug again and again.

So that's what we asked, the question, What elements in the dopamine neurotransmitter system are involved, if at all, in drug addiction? So we investigated, in the same subjects, we investigated three different elements that are involved in dopamine signal neurotransmission. One of them is the dopamine transporters, which we were using as markers of the dopamine terminal. This is an image of dopamine transporters. Forget about them, because while they are affected in certain addictive diseases like methamphetamine, these arrangements are basically secondary to neurotoxicity of these drug and dopamine terminals. But this is not found in alcoholics, is not found in cocaine abusers.

On the other hand, this other element, the dopamine D2 receptors, which is one of the dopamine receptors that has been shown to be involved in the translation of the dopaminergic signal induced by salient events into the required centers of the brain, or the motivational centers of the brain. And the dopamine D2 receptors similarly had been linked with the reinforcing effects of drugs of abuse such that if you block them by giving neuroleptics, you profoundly affect the reinforcing effects of drugs such as . . . basically almost any drug. And also if you create knock-outs that don't have dopamine D2 receptors you profoundly disrupt the reinforcing effects of various types of drugs in these animals. So dopamine D2 receptors are actually one of the ones that I'll concentrate [on] because they are affected in similar ways by a wide variety of drug addictions.

And finally, in the same subjects we measure brain glucose metabolism because [under] normal physiological conditions, the main source of energy for the brain is glucose. So then by measuring the different levels of glucose consumption you can actually get an indication of how active the brain is, and it's very sensitive actually to dysfunction, to the arrangements in brain activity. So I'm going to concentrate on dopamine D2 receptors and brain glucose metabolism.

**Dopamine D2 Receptors in Cocaine Abusers**

What did we find in dopamine D2 receptors? This is one of our first studies. It was done in cocaine abusers that were hospitalized to ensure that they were not taking the drug. And they were tested with spiroperidol. All of these are males. And first I'll show you the images and then I'll show you the numbers, the individual numbers. This is the scale to the right, and methylspiroperidol is a ligand that binds both to...
dopamine D2 receptors and serotonin receptors. But this binding to these receptors has different pharmacokinetic properties. So by waiting, say, two hours, you can eliminate mostly the signal that is coming from serotonin and your signal reflects dopamine D2 receptors. So these are different levels of the brain going at the planes where you have the basal ganglia from the upper part to the lower part, and in the posterior aspect here is the occipital cortex part of cerebellum where you have no activity because that area is, for practical purposes, devoid of dopamine D2 receptors. So this is a normal subject. You see the high activity into the basal ganglia.

Look at the cocaine abuser one month after last use of cocaine, and you can, just by looking at the images, see a significant reduction in the binding of the radioligand. And this reduction persists long after the patient has stopped taking drugs. And in this case we kept the patients for four months in the hospital to ensure that they in fact were not taking drugs. And we documented effectively cocaine abusers had disruptions, decreases in dopamine D2 receptors, that are long-lasting and certainly persist at least after four months of last use of the drug.

This is an image . . . the next slide basically shows the data but in a quantitative fashion. So you draw a region, you actually measure the concentration of your radio tracer and do appropriate mathematical modeling that then allows you to extract an indication of the receptor numbers in that particular area of the brain, or what we call receptor availability.

And so here it is, the measure of dopamine D2 receptor availability for normal controls in pink and for cocaine abusers in green. What I'm doing is I'm plotting it as a function of age because as we grow older the expression of dopamine D2 receptors is significantly reduced, approximately 4 to 6 percent per decade. So you see that reduction in normal controls, but you also see it in cocaine abusers. And if you look at the data as a whole you can realize that as a group cocaine abusers have significantly lower levels of dopamine D2 receptors. And this was significant. We've replicated that same finding in three different groups of cocaine abusers. Here at Columbia University, Marc Laruelle and his group has also documented the same finding. Others have used SPECT and [inaudible], also documenting reductions in dopamine D2 receptors.

However, I want you to look at the data and realize that this is not a categorical distinction. And it's something that has always intrigued me in terms of what does it mean to have a finding that it is statistically significant, but where there is overlap between your disease population and your normal controls? And, for example, look at this subject here with the normal control who indeed has lower levels of dopamine D2 receptors as those levels similar to those of cocaine abusers. So when I get data like this the way that I interpret it is to say that while as a group cocaine abusers do have lower levels of dopamine D2 receptors, and this in turn may tell me something about propensity for taking drugs and addiction, it certainly is also telling me that it is not sufficient to account for addiction, because if it were
sufficient to account for addiction then how do you happen to explain a cocaine abuser with levels that are normal or a normal control with levels that are lower? And I'll come back to that statement because I think it gives us an insight into what the significance of the differences in the receptors are with respect to addiction.

The other thing about these findings of decreases in dopamine D2 receptors in cocaine abusers that, as I say, is a very replicated finding, it is significant but it is not perfect, it's not categorical. The other aspect about it is it's not specific for cocaine. We and others have documented that dopamine D2 receptors . . . these are controls, this is just an illustrative pair of a control and an alcoholic. Measurement is with C11-raclopride, a ligand that binds to dopamine D2 and dopamine D3 receptors, the scale for dopamine D2 receptor availability. So we and others using different types of radio traces have documented that alcoholics that have a family-type history of alcoholism also have reductions in dopamine D2 receptors. We have also shown heroin-addicted individuals have decreases in dopamine D2 receptors. And we recently documented the same thing for methamphetamine addiction. So across a wide variety of addiction, excluding nicotine—in nicotine we and, I think, the group here at Columbia, that's one of the addictions where this does not seem to be consistent—but otherwise in cocaine, in alcohol, heroin, methamphetamine, this is a consistent finding.

The Role of Dopamine D2 Receptors

Now if you have a reduction in dopamine D2 receptors, and as I was saying, how does it help us in any way identify how this could translate either . . . two possibilities, I'm putting it as two possibilities. Number one, if you have low levels of dopamine D2 receptors, as it appears from the cocaine abusers, you could say could this be making you more vulnerable? It's not obviously per se making you addicted, but it could make you more vulnerable for addiction. But let me be again subversive and say the other completely different possibility, which is maybe it is not that the low dopamine D2 receptors are making more people vulnerable, maybe what's going on is having high levels of dopamine D2 receptors is protecting individuals to take drugs. And let me then go through where my thinking is going here.

So if you have low levels of dopamine D2 receptors or high dopamine D2 receptors, what simple explanation can you make? Well, when you have . . . this is a dopamine synapse . . . I mean the dopamine cells are not there for us to take drugs. The dopamine cells are to signal saliency. So the probability when the dopamine cell fires in response to a stimulant, the magnitude of how intense the stimulant is will determine the magnitude of how much dopamine is released. And then there is a probability of dopamine interacting with receptors. And that probability is not infinite, is basically quite fixed. And it is fixed because dopamine is liberated from the synapse but it's immediately brought back, is recycled back, into the terminal by these dopamine transporters. And mathematicians had modeled actually how long those dopamine stay in the synapse, and it has been
estimated that any given molecule of dopamine does not stay in the synapse for longer than 50 milliseconds. So the time at which dopamine has to interact with the receptors is limited. So then the question that follows is for a given . . . the same type of increase in dopamine what basically will determine the probability of an interaction for the same amount is going to be determined basically by the number of receptors.

So if—as in a question like this one—you have even a dopamine signal that is very mild, you have a lot of receptors, the probability of an interaction is quite large. On the other hand, if you have the levels of receptors are decreased the probability of an interaction is decreased. So this is the way that we simply try to understand what the significance will be of having a decrease in receptors. The way that I would view it is it would make you less sensitive to the signaling of stimulants that are salient, because the probability of an interaction would be lower. And I'll come back to this and how then this can make someone more vulnerable, if it is the case of vulnerability, or alternatively if it's protective.

Now one of the aspects that I started with is that in the neurobiological changes that were documented in addicted people, we really do not know if these were there before they starting the drug. We don't know if the receptors were already there or whether chronic drug exposure leads to these decreases in receptors. And this is not a trivial question because it pertains, to me, to one of the most challenging questions that we face in the field, which is to understand why people, when exposed to the same drug, to the same environmental conditions, some become addicted and others do not. And it pertains very much to issues of genetics as well as biological developmental exposures that you may have encountered while growing up.

So how do you address this particular question? Well of course it would be ideal to take people and measure dopamine D2 receptors before they become addicted, and then to actually follow them and then wait until they become addicted and test them. But you may realize that that basically is a very impractical proposition to start with because drug addiction starts in adolescence and it is basically very difficult to use this type of nuclear-medicine technology to image adolescents. And moreover the cost of such an experiment would be prohibitively expensive. So how do you tackle it? And we decided to tackle it in a different way. This is . . . basically what you're seeing here is a scattergram for another one of the studies. I've told you we've replicated the studies comparing dopamine D2 receptors in normal controls and cocaine abusers in three different groups of subjects. And we do that with imaging because with imaging technology you can not gather large numbers, so you need to replicate a particular finding to ensure that it was not just due to a sampling of subjects. So this is one of those studies. These patients were also inpatients. They were studied three weeks after the last use of cocaine, and you see in this case it's a C11-raclopride study. You see exactly the same finding: cocaine abusers as a group have lower levels of dopamine D2 receptors. But I want you to basically again see the overlap. Look at these normal controls whose
values are really undistinguishable from data from [a] drug-addicted person. So I want you now, having mentioned this fact that this is very similar to this of the cocaine abusers, I want you to forget completely the cocaine abusers and look at the normal controls. And what always has fascinated me about the normal controls is the wide variability in levels of dopamine D2 receptors that we observe in healthy normal controls that are not addicted to substances. And even though some of that variability is accounted by age, you can also see that it is not the only variable explaining the variability. Look at these subjects, their years of age, and this one here has 50 percent higher levels of dopamine D2 receptors.

**Receptor Levels and Drug Response in Nonaddicts**

So we decided to take advantage of this variability in the expression of dopamine D2 receptors to ask the question, If indeed we're postulating that levels of dopamine D2 receptors, either by being very low makes you more vulnerable, or alternatively by having high levels may protect you, then what does it mean to be a person that has low levels of dopamine D2 receptors vis-à-vis the way that you respond to a drug of abuse? And this is a nontrivial question because, if we are indeed seeing and implicating these receptors in drug addiction, it follows that it should have an effect on the way the levels of expression of these receptors it follows, we hypothesize, should have an effect on the way that people respond to drugs of abuse. So that's the way that we decided to address the issue of the extent to which differences in dopamine D2 receptors before a person becomes addicted in any way affects their responses to drugs.

We did a very simple experiment. We again replicated it twice, but the first one, which is the one that I'm going to be showing you . . . we took 23 healthy controls, we measured levels of dopamine D2 receptors, then we brought them back to the laboratory and we injected them with intravenous methylphenidate. Intravenous methylphenidate—which is basically methylphenidate, is Ritalin, which is the most widely used psychiatric drug in the treatment of attention deficit disorder—is pharmacologically very similar to cocaine, like cocaine blocks dopamine transporters. And when you give methylphenidate intravenously to cocaine abusers, in fact they like the drug very much, and they say it's actually very similar to cocaine, not the same but very similar.

Interestingly when you give intravenous methylphenidate to healthy controls, approximately half of them report the drug as very pleasant, and the other ones report the drug as very unpleasant. So the responses to stimulant drugs in people that are nonaddicted to drugs, whether you call it methylphenidate or amphetamine, is quite varied. And this has been described both in the animal as well as in the human literature. So we decided to ask that question, the question of do the levels of dopamine D2 receptors in the human brain in any way regulate the responses to stimulant drugs? And so we measured 23 healthy controls' dopamine D2 receptors, we injected them with intravenous methylphenidate, and we did a [inaudible] of self reports of drug effects. But our main variable, dependent
variable, was, is the drug experienced as pleasurable or is the drug experienced as unpleasant? That was the first [inaudible]. And what we found was as follows, indeed the availability of dopamine D2 receptors in fact affected the type of responses that subjects were given. And here it is. First look at the images, these are a subject that's reporting the effects of methylphenidate as unpleasant. This is a subject that [is] reporting them as pleasant. The images have been already transformed, so the numbers reflect availability. And you see this subject that reports it as unpleasant in this particular . . . for this comparison of this group, has significantly higher levels of receptors that this one here. And as a group you see this is quite significant. In individuals that are reporting the effects of methylphenidate as unpleasant, and it was very unpleasant, have significantly higher levels of receptors. Those that are reporting it as pleasant are significantly lower. And in life there are always outliers, so I have two outliers to the right that we have to ignore because I don't have time.

But I'm going to come back to this one here and ask the question, so why would that be so if you have such a finding? And the first thing why it would be so is—again I go into the preclinical literature to try to get an explanation—and what you find in the literature in reinforcement and investigation of reinforcing [inaudible], what it has been shown, for example, is if you produce an electrical current into the lateral hypothalamus, the electrical current is perceived as pleasant or reinforcing by the animal—I shouldn't call it pleasant—reinforcing by the animal, and the animal will press a lever in order to deliver the current. But what investigators have also shown is that if the current is too low it is insufficient to generate that response so the animal doesn't bother and does not press the lever. But what's fascinating is if the current is too high the animal stops pressing the lever because the current becomes aversive. So there's an optimal level of stimulation by which the activation appears to be reinforcing and makes the animal press the lever.

So if you use a similar type of analogy it follows that you could say, perhaps the reason why, in individuals with high levels of dopamine D2 receptors, methylphenidate is experienced as unpleasant is because when you inject intravenous methylphenidate, and this has been studied in animals, the magnitude of the increasing dopamine is at least five- to tenfold higher than that of any natural reinforcer. Not only is it significantly higher in magnitude, but that duration of dopamine in the synapse is also significantly, significantly longer. So could it be . . . the way that I would interpret it is in the simple way, the first go-around, is that when you have a lot of receptors when you take a drug of abuse—and drugs-of-abuse characteristics is that increases in dopamine are very, very large, they are supraphysiological—that increase is perceived as aversive because you have so many receptors it's overstimulated. On the other hand, if you have low levels of receptors, those low levels basically are able to blunt the large increases in dopamine, bringing the stimulation to the level, to the threshold, that is perceived as reinforcing.

High Receptor Levels and Averse Drug Response
And this is what we hypothesized. We hypothesized that perhaps the reason why this was occurring was indeed because, in this case, is what the supraphysiological increases in dopamine led to an aversive response. So we decided to test it and we said if our hypothesis is correct then it follows that the reason why these subjects are perceiving this as aversive is that the dose was just too large. What about if we get one-tenth of the dose? So we went to the IRB, we asked permission, and basically the rationale was we want to bring these subjects back, give them one-tenth of the dose, instead of 0.5, 0.05. And we hypothesized that that dose will be perceived as pleasant in these subjects. So we got the IRB approval, which took many months. And so finally we got the approval, we called the subjects and the subjects refused to come back because their response to methylphenidate had been very aversive, it had been aversive to the point that we had to report that to the IRB. So I don't know exactly whether on that level the hypothesis was correct. I think it was, that basically we were dealing with too large of a dose. But it is a characteristic of drugs of abuse, whether the doses that you take it and kids are exposed to, they are inducing supraphysiological responses. In this case low levels basically are not going to be leading these very aversive responses. And so when you, as a kid—because as I told you most drug addiction starts during adolescence—are exposed to a drug and you're exposed and you take it and say this feels good. And then the next time that you are in a party and they give it to you the likelihood that you will take it is much, much higher—and this has been shown by behavioral studies— than if [when] you took that drug the experience was so unpleasant that you refuse to come back. So if the kid gets the drug and basically gets a very aversive response, the likelihood that he will take it again is much lower. So you could then bring this up and say could it be that this is one of the mechanisms by which indeed . . . that having low levels of receptors make you more vulnerable because you will not get an aversive response. So that's what we hypothesized.

Now when you are doing imaging studies like this one you are limited. You are limited because you can not manipulate variables like you can in laboratory animals. So you are limited to the notion of replication. We've replicated exactly the same findings and show indeed that individuals with high levels of receptors have very aversive responses to methylphenidate and this is consistent whether you study them on different days. However, this is an association. How do you assess whether in fact there is a causal link, and what do I mean by a causal link? I mean whether indeed having high levels of receptors is causally linked to having an aversive response. How do you demonstrate that causal link in human studies?

Well the way that you would demonstrate that causal link would [be] you have these subjects in whom you have low levels of dopamine D2 receptors. If they are causally linked to aversive responses, if you increase the levels of receptors then that experience when you gave them the drug should be aversive. The problem is how do you increase dopamine D2 receptors in a human brain in a noninvasive way? And I don't know of any way to do it. However, you can do that in animals.
And so this is an example of how we’re blending—which was elegantly illustrated in the talk earlier—human findings to then design animal studies to then try to extract the pertinent information. So we asked the question, We can not do it in humans but if in animals we basically train them and make them addicted to drugs and then in the same animals, then, when they are already self-administering the drugs in a compulsive fashion, we increase the levels of dopamine D2 receptors, do we affect the self-administration of the drug? And that's what we did. And the study was led by Dr. Peter Thanos and this was the first study of this that he published, then doing others of this type. And this study . . . he was then a postdoc at Brookhaven National Laboratory, and he trained the Sprague-Dawley rats to self-administer alcohol. And when these animals were readily self-administering alcohol he then injected them with an adenovirus stereotactically into the nucleus accumbens. And in the adenovirus he basically inserted the dopamine D2 receptor gene. When you do that basically what results is a significant increase in receptors.

So this is the day of the injection of the vector. At day four receptors are 50 percent higher in the nucleus accumbens. The receptor overexpression is short-lasting, and that has to do with the fact that the vector was an adenovirus that does not integrate into the DNA, so its expression is very limited. And at day twenty, so the receptors go back to baseline around day ten. By day twenty he injected them a second time and then you can see it again. The receptors are increased again. And then he asked the question, In these animals in whom their dopamine D2 receptors are overexpressed in the nucleus accumbens, what happens to the self-administration of alcohol? And what happens is quite fascinating. It was dramatically reduced but it was not abolished. And you see it here, percent decrease in alcohol intake, approximately at four days, when you have the maximal increases in dopamine D2 receptors. It's almost 70 percent lower than when it was at baseline. It does not abolish it, it dramatically reduces it. And by day ten and twelve it’s gone back to baseline.

When he injected the adenovirus again, again alcohol drinking behavior went dramatically down. And those were animals who were injected with the adenovirus, also into the nucleus accumbens, but the adenovirus did not carry the D2 receptor gene, and this was important to do because you wanted to be sure that the changes in behavior were not a function of inflammation from the adenovirus. And it basically shows that without the gene it does not have an effect.

So this particular study shows that indeed, in animals, overexpression of dopamine D2 receptors dramatically reduces alcohol intake, and does provide evidence that high levels of dopamine D2 receptors indeed may be protective, not just in general of not taking drugs, but protecting you against taking high doses of a drug, which is ultimately what leads to addiction—high doses of the drug—because we all control—more or less, if we're not alcoholics—how much alcohol we take. And so you see, these animals . . . it's not that the alcohol has been inhibited. What's also fascinating, and the study just came out this month, is that he's taken this particular study and now replicated it not in Sprague-Dawley but in animals that are
genetically inbred for their propensity to self-administer alcohol. And these are the preferring alcoholic rats. These rats rapidly start drinking alcohol and they prefer it over other substances. So in these animals we don't know which are the genes involved in these behaviors but they are genetically inbred for these behaviors, so there are genes linked with this propensity to self-administer alcohol. In these animals increasing dopamine D2 receptors also significantly reduced the alcohol intake, indicating something that to me is quite fascinating, that certainly dopamine D2 receptors per se are not accounting to addiction, not at all, but they may be modulating and regulating your propensity to become addicted or severely addicted depending on whether you have the genes or you have the environmental interventions that may then lead to the addictive process. And that's how I basically right now view the process of the dopamine D2 receptors.

**Brain Function and Dopamine D2 Receptor Levels**

Now the question is why is that so? I was speaking about sort of hypothesizing that what's happening is that [if] you have low levels of dopamine D2 receptors this will lead to . . . then lead to changes in the signaling to the circuits that are then responsible for motivation, for drive, as well as other cognitive operations. So we decided, as I said, in these subjects in whom we have also measured dopamine D2 receptors we can also [measure] brain glucose metabolism. And we had done that to actually address the question, are the changes in dopamine D2 receptors in any way reflected with brain glucose metabolism?, which as I say is an indicator of brain function.

So in the next slide what you're going to see first is . . . now you're not going to see images of dopamine D2 receptors but brain glucose metabolic activity in controls—three different levels of the brain. By the way these are basically . . . this is the lower level, one of the lowest levels of the frontal cortex, the area we call the orbital frontal cortex. And these are sequential planes, going from lower to up. And this is the scale. And this is a normal control, this is a cocaine abuser's. And what we found is cocaine abusers have significant disruption, particularly in frontal cortical regions. And of them two of the most affected regions are the orbital frontal cortex and the cingulate gyrus. And moreover, abnormalities in the orbital frontal cortex and anterior cingulate gyrus are not specific neither for cocaine, are also observed in marijuana addiction, are also observed in alcoholism, and in methamphetamine addiction. And these are just the values for the group, so they're significantly lower.

And so then the question was, Are these changes in metabolism in any way associated with the changes that we saw in dopamine D2 receptors? And the answer is yes, indeed. And this is the slide showing that we basically scanned the whole brain, and then measure metabolism in 33 brain regions, and then identified those brain regions for which the correlation between D2 receptors and metabolism was significant. And that was basically mainly in cortical projections of the dopamine system. And the strongest correlations were at cingulate gyrus and orbital frontal cortex.
And this is the individual values, measures of metabolism in the orbital frontal cortex, measures of dopamine D2 receptors. And you see it is the individuals with low levels of dopamine D2 receptors in whom we are seeing the decreases in brain glucose metabolism into the orbital frontal cortex.

And the same thing . . . this is a study that we replicated in methamphetamine abusers . . . the same finding. The subjects with low levels of dopamine D2 receptors are the ones that have decreased metabolism in the orbital frontal cortex.

And this was quite a fascinating finding because it took us by surprise. And it took us by surprise because in general most of the studies in drug addiction have concentrated mainly in limbic brain areas, and the frontal cortex was not considered to be important in the process of addiction. And what the imaging data basically threw at us was that one of the main areas disrupted with chronic use of drugs are the frontal cortical areas, namely orbital frontal cortex and anterior cingulate gyrus.

**Saliency and the Orbital Frontal Cortex**

Now why was this? This was perplexing. As I say, there was no data. There was one preclinical study showing involvement of the anterior cingulate gyrus. So it was perplexing because the frontal cortex had not driven the attention of people involved with substance abuse. However, the orbital frontal cortex had attracted the attention of those individuals investigating food-rewarding processes. And what these investigators had clearly shown was that the orbital frontal cortex is an extremely important area of the brain in signaling the saliency value of a particular stimulus. And they also showed [that] not only [is] the orbital frontal cortex an extremely important area in assigning saliency value to a stimulus, but also in changing that value as a function of a context.

Now why is that important? This is extremely important because when you have a reinforcer, a natural reinforcer, the value of that reinforcer is going to be affected by the context. And this was demonstrated very elegantly by Schultz, who, actually using electrophysiological technologies, was recording the cells in the orbital frontal cortex on primates. When you show a primate a piece of lettuce, it's salient and the orbital frontal cortex signals. But when you show that same animal the same piece of lettuce by the side of an apple, the lettuce no longer leads to firing of cells in the orbital frontal cortex, whereas the apple does. And he postulates that the reason why the lettuce is no longer able to activate the orbital frontal cortex is that the saliency value of this reinforcer when the apple is by the side is basically decreased. So that's the whole concept of the value of something is relative to something else. And that is driven by the orbital frontal cortex.
Moreover, what experiments had shown also in animals is when you destroy this area of the brain, when you damage it, something fascinating happens. When you take a stimulus you can actually make an animal press a lever for something that is reinforcing, so the animal presses a lever and basically gets food and presses the lever. But then the investigator removes the food and what the animal does is he stops pressing the lever. However, if the investigator damages the orbital frontal cortex something fascinating happens. The animal learns very rapidly to press the lever, just as if he were intact, or she were intact, so he presses the lever. But if the investigator now removes the food the animal continues to press the lever again and again and again, even though that lever is no longer reinforcing. In other words, the animal has lost its ability to change the value of what originally was a salient event. And that continuing to press the lever again and again when there's no longer a reinforcement, indeed, is very reminiscent to what many of my patients tell me. They say, "Doc, I don't even know why I take the drug. It's no longer pleasurable. I just cannot stop taking it," indicating that indeed, perhaps the role of the involvement of the dopaminergic system is by disregulation of these areas of the brain that basically are crucial in driving our behaviors. Because this is the area of the brain that would signal ultimately when something is salient and behaviorally relevant for the animal to take into action. And the other area, the anterior cingulate gyrus, is an area of the brain that in the other side of it allows us to exert inhibitory control. So something is very salient, we want to do it, but we catch ourselves saying, "Uh uh, this is not a good idea." It is the anterior cingulate gyrus which will be able to stop us from doing it. So what we're postulating is that in drug addiction, disruption of the dopaminergic pathways leads to disregulation of these frontal areas that are key both in motivating our behavior and two, in allowing us to exert inhibitory control.

And let me just go through these ones very rapidly, because it's late in the day, and just end up with my last slide in terms of what have we learned with the imaging in terms of what the role of the dopamine system is? The dopamine system is not the only neurotransmitter involved in drug addiction, it's not at all. But what these studies have actually been showing us is that in fact disruption of the dopaminergic system is evident in a wide variety of drug addictions and that this disruption in turn is producing dysfunction in areas of the brain that are involved with motivation and drive, inhibitory control, also very likely reward, nucleus accumbens ventral tegmental area. And an area that I have not even had a chance to go into, for which the dopamine system is extremely important, is also in facilitating memories, both by conditioned responses through the amygdala, as well as normal memory process through the hippocampus. So what it brings forth to light is that the process of addiction is not producing a disruption just in one brain region or circuit, but that it implies disruption of multiple circuits that are accounting for that very malicious phenotype that leads an individual to take that drug at the expense of his own incarceration, at the expense of many times losing the family, at the expense of basically losing the job, even when that individual says that the drug is no longer pleasurable. So this is the circuitry that imaging
actually has documented, not just through these studies but others, to be involved in drug addiction.

Now how do we take this [inaudible]? Well my perspective is, if we know that these circuits are disruptions, this is important because it is telling us that when we are designing treatment we should start to basically develop treatment that will strengthen motivational drive circuits that would interfere with conditioned responses such that the individual will not have this intense drive to take the drug when exposed to it, and finally that can promote plasticity of dysfunction of these brain circuits that have been either damaged by chronic use of drugs or, alternatively, may have been dysfunctional from the beginning and have made a person more vulnerable for taking drugs.

So my end slide is, of course, this research has been the effort of a wide group of very talented investigators at Brookhaven National Laboratory, which from this would have not been possible, and of course with the general support of NIDA and the Department of Energy.

And I thank you for your attention.

Questions and Answers

Richard Mayeux: We have time for a few questions.

Man: Allan [inaudible] at Columbia. Nora, that was a wonderful talk . . . may I also say stimulating talk. Two questions: One is, is there a relationship between the degree of drug abuse and dopamine availability? And the second question is, Have you looked at relatives of drug users to see if they also have lower D2 availability?

Nora Volkow: Yes, the question has to do . . . is there an association between, I guess, the severity of the history of drug use and the levels and the availability of dopamine D2 receptors? And the answer is there is a relationship with years of drug utilization. The problem of that relationship is confounded by the fact that the longer the years you've been taking the older you are, so there is the confound of the age effect. So it's not clear cut. We have not seen a significant correlation with the doses of drug reported by the abusers.

Have we looked at individuals' families? Yes we have. We have looked at . . . specifically for alcoholics and these are experiments that we're doing in collaboration with Henry [inaudible] and Bernice [inaudible]. And what we've seen is quite fascinating, so we're studying these children who have a father who's an alcoholic and another first-degree relative who's an alcoholic. And we measured dopamine D2 receptors. These individuals are adults, they are not addicted to the drug but have a strong, strong family history. And to my surprise and horror, because I was counting on this on getting a grant, I was expecting that the
receptors were going to be low. The receptors were significantly higher than normal controls. And of course that makes writing for a grant much harder.

But basically you have to look at the data and say well, what type of explanation you can make to that, and again that's basically based on our animal studies. We said well, perhaps this individual, even though they may have the genetics, are not alcoholics because for whatever reason [they] have the high level of receptors that are protecting them. And so this is . . . we put it in as a hypothesis. It was our pilot data for a grant. But then at [inaudible] I saw a fantastic study which is much more powerful than ours, even though it was only seven subjects. It was Mark [inaudible] and what he was showing was looking at identical twins discordant for alcoholism. And he found was as follows: the alcoholic twin, as expected, low levels of dopamine D2 receptors. The discordant twin for alcoholism had significantly higher levels of receptors than normal control. So we found that in a much less powerful design, just looking at subjects, he is now finding this in identical twins, indicating that what we don't know is what is accounting for the increases in dopamine D2 receptors. The fact that his identical twins were discordant also in the levels of dopamine D2 receptors is telling you that the drive is not just genetic, that something, for whatever . . . we don't understand what it is. It's likely to have to do with issues such as stress from animal experiments. But again it's very tentative, what you can make of the explanation.

**Man:** What about nondrug addictions like gambling addictions and that sort of thing? There seems to be a sense, from what I'm gathering, that there's some sort of almost self-medication here to reach a desired level of stimulation. But have you looked at these kind of disorders?

**Nora Volkow:** We have. And I was intrigued very much because, I mean, my thinking has evolved, and like the previous speaker I've made some spectacular mistakes. So, but in a way one of the things that I was thinking . . . okay, low levels of dopamine D2 receptors, because that's what I started with thinking makes you more vulnerable. Now I think that high levels are protecting you. But so I was thinking that, that low levels made you more vulnerable. So I said well, is it just a function of chronic drug administration or do you see it in another type of condition where you have the same compulsive behavior? So we went for obesity. We went for obesity because it's a big-impact disorder. And what we found was actually quite fascinating, because it gave us some insight on a problem that has counted me . . . all of these have low levels of dopamine D2 receptors. What leads to the specificity of the drug as the reinforcer, right? And so we went to the obese people. These were morbidly obese patients—I think it was average 350 to 400 pounds . . . very difficult to do because they broke the camera. So we had to construct a new bed and after two years we succeeded. And what we found was the levels of receptor were significantly lower. But different from anything that we've ever seen in drug addiction was these individuals have increased hyperactivity in the areas of the brain, somatosensory areas of the parietal cortex, that are regulating perception of food stimuli. That was the lips, the tongue, the mouth; they were
hyperactive. And so what it gave me an insight . . . was in terms of why certain individuals with low levels of dopamine D2 receptors would go, for example, for a drug versus going for food? What it is keeping me, again, all of these are hypotheses based on data that you get . . . is that by having increased activity in these somatosensory areas it makes that person much more sensitive to the palatable aspects of food, which is one of the variables that would account [for the] hedonic properties of food. So it's more sensitive to that particular reinforcer so [inaudible] has low levels of receptors is going to be much less sensitive to other things. But the fact that it's hypersensitive to this one may drag him across this path. So that's where the insight came.

Now why is it that someone may, for example, take alcohol versus cocaine? There are individuals that take anything, but there are also individuals that will just stick to one drug. And you can start to understand that, that's where the specifics of the genetics may come around. Alcoholic subjects, it's not infrequent that they will tell you, "Doc you may want to believe me or not, but if I don't drink I just feel perpetually anxious. So as a result of that I function much better drinking." So then you start to understand why would a person choose heroin as opposed to cocaine? It is likely that there may be there particularities in terms of disruptions of those systems that make you more vulnerable. And here I'm just speculating, but bringing up the notion that genetics may come from other neurotransmitters and what dopamine may be doing is basically either protecting you or alternatively making you more vulnerable.

**Man:** This is a follow-up to his question. I'd like to know references to that obesity research that you mentioned. And taking the three elements of your last slide, change, reward, motivational system, interfere with conditioned responses, and promote plasticity of dysfunctional brain circuits, how do you apply that to an addiction, say like a food addiction?

**Nora Volkow:** Well how do you apply that? First of all, one of the aspects, let's say conditioned responses, they are extremely important certainly in drug addiction, and it's also certain that they are extremely important with food. I find myself always eating a chocolate when I go and pay for something even though I'm not hungry because I see that chocolate. So you are conditioned to respond in certain ways. So now if you can control it more or less you're okay. But when it becomes pathological in my brain it would be wonderful if we could develop a medication that will interfere with that conditioned response. So you ask the question, what type of studies have given evidence that this is possible? So I went back and I said, do we have evidence that you can interfere with Pavlovian conditioned responses? And the answer is yes, investigators have been able to do it. There are not many studies, but the few studies there are, they basically show that drugs that enhance GABAergic activity interfere with conditioned Pavlovian responses. And one of the things that's fascinating right now in terms of promising medications for the treatment of drug addictions are drugs that are enhancing GABA, have actually
shown to be beneficial in alcohol in humans, and have shown in multiple preclinical studies to be beneficial in models of animal drug self-administration.

So that’s an example of plasticity, and that’s, of course . . . again I’m being very ambitious, but I think we should be ambitious now that we have the technology, the tools, and we’re understanding the brain. We know that for many years investigators on learning disabilities have used training in order to make kids with learning disabilities able to learn and read better. But what these investigators have now shown with images is that they can actually lead to some recovery of brain function, and if not the same area, they actually can make other areas take over for the function that account for the improvement in reading. So I’m putting forth the same concept and say why can we not then, using the same strategy, design behavioral interventions to strengthen, for example, the anterior cingulate gyrus, which is one of the areas that allows us to exert inhibitory control? And there are many ways that people are looking at that: you could do it with behavioral interventions, you can do it magnetic stimulation like it's being done now with patients with stroke, but we haven't yet applied this type of strategy for a problem like drug addiction. But I’m just sort of putting it . . . these are potential things for which we now have the tools to start to utilize.

**Richard Mayeux:** Thank you all for your attention this afternoon. This concludes the afternoon portion. And thank you to our speakers.