Dr. Lightfoot: [music] So every year, we try to find folks who are just upcoming in their field and who are the rising stars. And I think our next speaker is one of those individuals. He's doing some really interesting work with dopamine now and combining a lot of different fields. So please join me in welcoming Dr. Jeff Beeler to the stage. [applause]

Dr. Beeler: Thank you. Good afternoon. Or I think I'm supposed to say howdy.

[Audience]: Howdy.

Dr. Beeler: Great. So standing here in the big Red Dot, I'm feeling really energized. And that's actually what I want to talk to you all about today, this feeling of having energy. So we've all had it. Sometimes you feel like you just have a reserve of energy. Other times, you're tired. But beyond that, these sort of passing transient energies, it also sort of has a more long-term persistent characteristic. So we all know people who seem to have an endless reserve of energy. We describe them as go-getters. They're tireless. They're simply energetic. And, of course, we know people who we might charitably-- people that are the opposite we might charitably describe as energy conservatories. And so the question that I want to pose is where does this sort of sense that we have, of having energy or not having energy, come from? So intuitively, we think this is almost a no-brainer question. We feel like we have energy when we have energy. And then when we get tired and our energy supplies run low, we don't. But what I want to do is highlight a couple of instances where this is not necessarily the case. And if you start to reflect on your own experience, you'll probably find that there's lots of disconnects between your feeling of having energy and what might really be having energy or not. So, one, how many people here have had an occasion where you have a really busy, challenging day? You just have one thing right after another. It's like a day of whack-a-mole in the office or what have you. And, yeah, sometimes that makes us tired. But have you ever come home, and after that, you just feel revved up and energized? You're like, "I can do this. Bring it on. I want more." Right? And suddenly, you're doing other stuff at home. Conversely, how many people have gone in and had a dull day, very little demands made upon you? You just kind of have to pass the time. And you get home, and you're kind of listless and tired and don't want to do anything.

So there's this sort of disconnect because in one case, you don't spend much energy, and yet you seem tired. And in the other case, you spend energy, and you feel energetic. So to take this to an even further or higher extent, so we all know those people - and there's probably some in this audience - who get up at like 5:00 in the morning or earlier and go to the gym and have a vigorous, strenuous workout. 5:00 AM? I'm not convinced the universe actually exists at 5:00 AM, but these people do that. And then they go to work bright and early, and they're chipper all day long. So if you have a lack of sleep, and you have a vigorous workout, actually, your energy reserves are probably, you would think, low. And yet, all the people who do this, they do it, and they report because they feel invigorated. Conversely, anybody who's had a job where you have to sit a lot during the day realizes that sitting can be exhausting. So just to give one last example of this sort of disconnect between sort of literally having energy and the feeling of having energy is obesity. So obesity is associated with inactivity and reduced activity. And it's not just because of having to move all that weight around. But, also, even when obese people start to lose weight, there's sort of a lingering inclination towards inactivity. But in this instance, the body has a surplus of energy. Right? There's clearly no shortage. And then the other hand-- I don't know if anybody here has ever gone an extended period without food like fasting. I sometimes forget to eat. I know. As Whoopi Goldberg said, "That's a special kind of stupid." But when I do that, I don't suddenly start to wilt. I actually feel sort of energetic. And, again, there's this sort of mismatch.

So what I really want to do is make an argument that when we feel we have energy and when we don't feel we have energy, this is not because we literally do or not. But it's neurally regulated. It's coming from something our brain is doing to us. So to get you into this a little bit more, I want to introduce this idea of micro expenditures. So all throughout our day, there's these hundreds, possibly thousands, of teeny little decisions we have to make to expend or not expend energy. And so sort of the classic example is the stairs versus the elevator. So I'm from New York City. Every day, you have the choice, "Do I take two flights of stairs to get out of the subway? Or do I wait in line patiently and let the elevator haul my carcass up 30 feet?" So it's a decision. Another one, you come home. You're tired. You sit on the couch. You want to relax, and then you're like, "Oh, I'd like a tasty beverage." Do you just bound up and go the whole 20 feet to your refrigerator? Or do you sit there and go, "Eh, maybe later"? All these teeny little decisions-- and what I want to point out about these is, first of all, they're cumulative. They sort of color your day. Actually, if every little decision like this, "Oh, I go do this. I go do this." Right? Or if every time you're like, "No. No." The worst example of this, I found myself scrolling through Facebook one time, and I wanted to like something. I'm like, "Ugh, God. I just don't feel like doing it." And I scroll forward. Yes, I couldn't move my finger to press the like button. Obviously, this is not truly an energetic problem. But what this really highlights, and what I think is important, is it reflects willingness to expend energy. And in my mind, this is the crux of the issue. So most people think - and it kind of makes intuitive sense - that if you have energy, that's what determines how willing you are to spend energy. I want to say that's exactly not right, and it's completely the opposite.

That feeling of having energy or not arises by whether or not we are willing or, more specifically, whether or not your brain is willing to expend energy. And this makes all the difference in the world. So the question is where is this regulated in the brain? And my work for the last 10 years has been focusing on dopamine. And so I want to tell you a little bit about that. Oh, I forgot. So just to clarify this energy thing, we all know that we have a homeostatic system that generates energy. And so we can view that as a power plant that powers the brain. And our feelings of having energy is like a fuel gauge in that power plant. And so that's sort of the common way people think about it. And what I want to argue, really, is that the brain, in particular, the dopamine system that I work on, is sort of the brain's comptroller. And what we really can think about this feeling of having energy or not as arising from the brain allocating energy to different things. And so it's not really a direct, literal translation. So getting on with it—so, dopamine, probably most people in this audience have heard about dopamine. And it's associated with a whole list of neuropsychiatric disorders, which I just included on the slide, I won't go over. But mostly, it's known as the reward transmitter. And it has, for a long time, been associated with-- I want to argue that dopamine's gotten a bad rap. It's been associated with compulsive behaviors like in addiction and obesity. And the idea is that dopamine is-- I like to call it the neuro id. It just drives you to do more things, "I'll take that drug. I'll eat that extra brownie," and so forth. But it's really not that simple.

So, for example, in both addiction and obesity, dopamine, over time, is actually reduced. And so it may well be that compulsive behavior arises from a reduction in dopamine. But that's actually not what I want to talk about today. I want to switch and talk about the role of dopamine in regulating energy. So for 50 years, as much as we've known that dopamine has been involved in reward, we've also known that dopamine can regulate behavioral activity levels. In fact, the drugs cocaine and amphetamine that act on dopamine and increase it really define the class of psychostimulants. So if you increase dopamine, you have more energy. And then when you decrease it, dopamine generally becomes lethargic, sort of slow-moving. And in the extreme-- so drugs that block dopamine, for example. And in the extreme, you can't even move. And that sort of gradually happens with Parkinson's disease. So let me back up a second. So just to highlight one example of-- there's lots of different studies that we've worked on to try to characterize the role that dopamine plays in a lot of our behavior and focusing on the role of energy management instead of reward. And I just want to highlight one real quick to kind of get across why I'm arguing that dopamine is playing an important role in really deciding how you allocate energy rather than driving repetitive behavior. So within obesity, there's this idea that's become prominent. And it's maybe in the last 15 years that obesity can be likened to addiction.

And so this is based on the idea that the dopamine receptor goes down, and then the lack of dopamine signaling causes compulsive behavior to sort of make up and compensate for that. So we knocked down the dopamine D2 receptor in mice to see if they would overeat. And I need to go through this really quickly. We also gave them wheels so we could asses the role of running. So the blue lines are the wild type mice. And the open squares on the top are the wild type mice without wheels, and they got fat. But the ones with wheels did not. But you can see the red line. These are the mice with the knocked down D2. They actually did not gain more weight. They didn't eat more. But, also, having the wheel made no difference. It didn't yield any protection at all. And the reason is very simple because these mice are lazy, and they really don't run. So, again, the red is the mutant mice. And you can see they run much less. So not only do they not have any protection against obesity, but they didn't have any protection against metabolic disorder as well. So this has basically led me and collaborators and colleagues to this dopamine thrift hypothesis. And that's that dopamine is a central substrate to manage energy and resources, behavioral energy allocation. And it's doing this to mediate behavioral flexibility and adapt your behavior to environmental conditions. So throughout evolution, animals had very little control over how much food was in the environment. But the one thing that they could control is their own choices and energy decision-making. So I have to move quickly. So what I've been talking about so far is the way that dopamine is affecting sort of ongoing behavior. But it's also known that dopamine affects synaptic plasticity and learning.

And so I just want to give you one example of that. So we used optogenetics in this study. And this one, we put a fiber optic in the midbrain. And when you turn on a laser it's connected to, it stimulated dopamine cells, long story short. And, yes, this is actually a rat for the astute among you in the audience. But a big white rat's easier to see than a small black mouse. So I used a big white rat. And so what we did is we put the mice into an operant box where they had to press two levers. One of them would turn the laser on. The other wouldn't. And others have shown this before that mice will repeatedly press the lever. But we wanted to test and see what would happen if one group was food restricted and the other wasn't. And what you have to remember is they're not getting anything for this. When they press the lever, they don't get a food pellet or anything. It just stimulates dopamine. So what I want to highlight from this slide, the blue are the mice that were food restricted. And this is their pressing across sessions. And the red are the mice that were not. And what you can see is that, first of all, all the mice press just because you're stimulating their dopamine. And it's a learning process. It happens over time. But importantly, the food-restricted mice press a lot more. And so my focus here and the reason for showing you this is not to talk about food restriction, per se, but the idea, first of all, that dopamine can have a profound learning impact. So it's really teaching these mice to do a completely pointless behavior. Right? And it's malleable. It's not fixed and rigid. So merely food depriving-- and they weren't starving to death or anything. But food depriving the mice a little bit really changed the learning curve and how much they performed.

What I want to make the argument with this allocation of resources then is that this has a pervasive and profound effect on our neurocognitive function. And it's a cumulative one. It controls how much, overall, we expend energy. It controls how we direct that energy and our decision making. So one of the problems that anyone faces is, "Do I expend my energy on things I know are rewarding and have been productive in the past, or do I try new things?" That's called the explore-exploit dilemma. And dopamine regulates that as well and, of course, learning rate. Right? So how quickly do you adapt, and how quickly do you update your knowledge? If you have a great route to work, and it's always traffic-free, one day you get stuck in a traffic jam, do you just completely stop taking that route? Or do you continue? But then how many times does that traffic have to get backed up before you decide, "Well, maybe I should start looking at a different route"? So this is called the learning rate. And dopamine plays a role in that too. So, basically, what I want to argue is that dopamine going through these three things really affects our day-to-day behavior across the board in many, many different domains of life. Real quick, so how does socioeconomic status affect dopamine? We haven't really studied it. We've studied dopamine in addiction. We've studied dopamine in Parkinson's. But how does being in a scarce environment, having to work three jobs-- how does the dopamine system adapt? And does that change your behavior? And how does that pervasively affect sort of a number of neurocognitive functions? Across aging, dopamine tends to decline. This is not just in Parkinson's. Just in normal healthy people, dopamine goes down. How does that change, again, our neurocognitive function? How does it change explore-exploit energy levels and so forth?

And finally, appropriate here, is exercise. So exercise, I find, is really interesting because it's the expending of energy, but everything that I can see, it seems that when you do it, it makes you want to expend more energy rather than conserve. So it has this sort of paradoxical effect. And how exercise effects dopamine really seems to be complicated and not completely clear. However, I do think, overall, that the data is pointing towards it sort of up-regulates it. So exercise, consistent with feeling invigorated and so forth, is going to generate more energy expenditure. So I'll terminate there. I've gone a little bit over. So the reason for neuro qi is-- if anybody studied martial arts, qi is the internal energy. And with training and cultivation, you can focus that. And the argument here is that really the dopamine system's a primary substrate in the brain that is doing that for your energy. And it's determining how you allocate your energy towards what and that this has a pervasive effect across your life. There's a number of people who've been involved through this throughout. Thank you very much. [applause]

Dr. Lightfoot: Thank you, Dr. Beeler. Great job. We have several questions. The first one is from Monica P. at Texas A&M-San Antonio. And it kind of comes with the first part of your talk. She asked, "If dopamine levels are up, is it impossible to have low energy?"

Dr. Beeler: If dopamine levels are up, is it impossible to have low energy? So I think that speaks to what I'm talking about with the disconnect. So I think if dopamine levels are up, it's probably impossible to feel like you have low energy. And, in fact, that's sort of the case in point is when people actually do start to get tired, drowsy, and have low energy-- in fact, it's becoming a bit of a problem. College students, people who do startups. What do they do? They take Adderall or Ritalin, which increases dopamine, and you no longer feel tired or sleepy. So I think the answer is your actual energy levels can be up, and you can very much feel like you're not running out of energy. And that's because dopamine is changing that.

Dr. Lightfoot: This same question, we've gotten various forms of this. And, basically, it revolves around the question can you increase dopamine usually through food or some supplement? In particular, we got one question from Mick here, "How does dietary intake of tyrosine influence dopamine?"

Dr. Beeler: I have to actually confess to not being an expert on that. My general understanding is that it's not very easy to manipulate dopamine in a diet without completely-- if you get rid of all tyrosine, these sorts of diets. So I don't think that that is a particularly easy way of manipulating dopamine.

Dr. Lightfoot: So it's difficult? We shouldn't all go out and eat broccoli or anything like that?

Dr. Beeler: No. I'm not aware that this is particularly helpful.

Dr. Lightfoot: Okay. So I'd like to ask you a question about it. How difficult has it been to put forward your ideas with all the ambiguous results out there? We've done some of this work, and one study we get one thing. Another study, we get another finding, especially with all the different receptors. And it relates to a question that we had. We had one question about can we increase dopamine 2 receptors naturally?

Dr. Beeler: Yeah. So I think the answer to that is probably yes. And so right now, as you know, I'm interested. And we're looking at how exercise may, in fact, sort of up-regulate the dopamine system. So, for example, a collaborator of mine, Giselle Petzinger, has done work. They look at exercise and Parkinson's. And in their Parkinsonian mice and rats, when they exercise them, that actually increases, well, the receptor level. The dopamine cells are actually dead. So we can't increase them. So I think there are ways. And, in fact, one of the things I'm really interested in is, I've mentioned, environment, right, so an enriched environment versus a poor environment. And, to my knowledge, we have no idea whether changing the sort of wealth of the environment would change dopamine. And I kind of suspect it does. But we don't know. So in answer to your question, there's all sorts of different contrary results. And dopamine is very complex, and it sort of has many faces. And the field, in general, is struggling and also going through a renaissance. There's just new remarkable data coming forth. And so I think people are struggling on how to put this all together and what to make of dopamine. And the sort of idea that it's just reward is, I think, gradually slipping. And the big battle between is it motivational and learning, I think, is starting to lose prominence. And people are kind of asking, "What does dopamine do?" And I'm a big fan, obviously, of what I'm talking about, that it's really a resource allocator. And it's an idea that's coming up from other people as well now.

Dr. Lightfoot: A lot of puzzle pieces out there. We just got to put them all together.

Dr. Beeler: There are. Yes.

Dr. Lightfoot: Excellent. Thank you so much for your talk.

Dr. Beeler: Thank you very much.

Dr. Lightfoot: Please join me in thanking Dr. Beeler. [applause] [music]