Key:

G: Dr. Gordon

K: Dr. Koroshetz

G: Hi, I'm Joshua Gordon, Director of the National Institute of Mental Health.

K: And I'm Dr. Walter Koroshetz, the Director of the National Institute of Neurological Disorders and Stroke.

G: We're here to talk to you today about the future of neuroscience in particular of the NIH and actually the US government's BRAIN Initiative. BRAIN is actually an acronym, it stands for …

K: Brain Research through Advancing Innovative Neuro Technologies.

G: And the BRAIN Initiative is really focused on trying to understand how the brain produces behavior.

K: And I'd say that the necessity to do this is, is really easy to understand. If you think about people who suffer with disorders of the brain, the symptoms that the patient experiences are due to dysfunction in brain circuits. And this occurs in neurological disorders and it occurs in psychiatric disorders, substance abuse disorders. The problem that we have in trying to alleviate these disorders is that in most cases we cannot see the cause of this symptoms, we can't see the dysfunction in the neural circuits.

G: Yeah, that's well illustrated by the difference say between a classic neurologic disease like stroke, where you can see with the brain imaging or by examining the brain after death damage to a particular area of the brain. And through studies of stroke patients, we've understood that different things happen in different parts of the brain. The visual part of the brain governs your ability to interpret the visual world, the forward part of the brain, the prefrontal cortex though is a little bit more difficult to understand but it generally regulates behaviors, cognitions, emotions and etc. The problem is that in many neurologic and psychiatric disorders you can't see a lesion in the brain, you can't see something wrong. And what we know from lots and lots of study is, that the function of the brain is disturbed in these disorders, but we don't know precisely how that function is. So, the BRAIN Initiative seeks to develop tools, first by studying them in animals and then eventually in humans that will allow us to see that dysfunction in the patterns of neural activity in the brain that produce abnormal patterns of behavior.

K: Right, Josh. Josh gave the example of stroke where we can see what the lesion is in the brain and that causes the patient's deficits but the really interesting part of stroke is trying to make the patient's improve over time, to the best of their possible ability. And what we know is that people do recover after a stroke, after a traumatic brain injury, it takes time. And we think what's happening is the brain is rewiring to give people that function back but we don't really understand how that happens, we can't see how those new wires develop, or how signals are taken through those new wires. And then on the other hand, we have diseases which we think are caused by abnormal rewiring of the brain. So chronic pain and substance abuse, opioid addiction, we throw into that camp where we think the exposure to heroin really completely rewires the reward system in the brain changes these functional connections. But we don't really have a good way of seeing that. And so, without being able to see what the problem is, it's really hard to make a difference. And that's, I think, the impetus for the BRAIN Initiative that NIH is leading.

G: The BRAIN Initiative has several different components. The first component that we're probably the furthest along with, is called the brain cell census. The idea here is that the brain, like the rest of the body, is made up of cells, and the brain those cells are called neurons or glial depending upon whether they're performing the calculations themselves or they're supporting those calculations by providing the proper environment in the brain. Neurons and glial though, are not just two cell types, there are hundreds, maybe thousands of types of neurons and there are also a number of different types of glial. And we need to understand which types there are and where in the brain those types are, if we are to hope to be able to watch, to be able to visualize those different cell types and how they go awry during disease. The brain cells census is an effort to identify all the different cell types in the brain and figure out where in the brain each of those cell types are and in what number etc. and also to develop the tools so that we can observe those specific cell types in action and modulate the activity of those cell types to try to correct any differences in activity that we might see in disorders. The brain cell census is actually not just one research project, it's a number of research projects scattered across many institutions across the United States. The idea is to build an atlas, a computerized atlas of the brain so that we can know what all the different components are. So that's a first step that we're taking with the BRAIN Initiative.

K: As Josh mentioned, the cell census project is kind of like if you're trying to understand the computer, or at least getting out all the different parts of the computer, which has all these different cell types. As we said the BRAIN Initiative is focused on building neuro technologies to allow us to understand how these circuits work and just the example so there are 85 billion neurons in the human brain. Trying to get to classify 85 billion neurons is not technically possible at this point. But before the BRAIN Initiative, it was a massive project to classify 400 neurons, but technology's improved and now people have developed automated methods to classify millions of cells at a time. These new technologies now give us the possibility to actually do this in the human brain. Our staging for the human brain project is a project to identify all the different cell types in the mouse brain which has about 8.5 billion neurons. And then as Josh mentioned, it's not just a cell census in terms of a list but the cell census gives us characteristics of particular genetic drivers that are in cell type specific cells. And the new technologies we have now which merge physiology with genomics allows us to use the genomic information to put into those cells engineer genes that say, make those cells light up when they become activated or make those cells become dormant when we shine a light on them or give them a particular chemical. We have the ability to access the cells as precisely turn on or turn off these cell types once we understand what they are and that is the tool we need to really examine circuits and their relationship to behavior.

G: If we're going to be able to examine those circuits and their relationship to behavior, we don't just need to know what the components of the cell circuits are, what different cell types are, but we need better tools to be able to observe and modulate these neurons. On the observation side, the BRAIN Initiative has sponsored a number of projects to look at better ways to measure the activity of neurons, and not just a few neurons at a time, which is the height of technology say 10 or 20 years ago or 100 or 200 neurons at a time which is the current state of technology, but really pushed to the point where we can look at thousands or tens of thousands or even hundreds of thousands of neurons at the same time. Why? Why do we care about being able to observe the activity from lots and lots of neurons all at once? There are, as Walter mentioned, billions of neurons in the brain and in order to perform any one function, many, many of those neurons tens of thousands perhaps need to be active in just the right way. And unless we can measure that many, we won't really be able to understand the neural code that is, how neuronal activity produces behavior. And if we don't understand that code then we can't understand how that code breaks down a disease. There are a number of labs looking at tools like advanced microscopes, advanced optics, etc. to be able to monitor the activity of, as I said, tens of thousands of neurons all at the same time. And a number of other labs that are developing advanced techniques with micro electrodes that will enable us to record that activity electrically as well. We try these different approaches, because we're not really sure what the best way to do it is going to be and what's going to make the most progress over time. So, we invest in a number of different approaches to see what's going to work best.

K: These technologies are exploding. And that's not an exaggeration that the expectations have been met and exceeded by bringing in engineers, physicists, chemists, mathematicians, into the BRAIN Initiative. But as we have stated explicitly-

G: In fact, Walter, in the latest round of grants that we gave out last year, there were more grants to engineers and physicists than there were neuroscientists.

K: That's correct. And that's really what's helped us is to open the door to neuroscience because there is, we think, an inherent draw of people to try and understand the brain and to take part in this exciting initiative, I think, has been very attractive. Now, many of the tools and most of the tools that we are developing are developed for use in animal models. So, the exquisite ability to measure the activity of tens of thousands of neurons is now possible in the mouse. And we're learning things about how circuits work and the push now is going to be trying to understand how do you take this information that we're getting from the animal models and apply it to the human condition. The BRAIN Initiative is working bottom up, but it's also working from the human as well. And so, we have a number of projects where we are using technologies that are now currently available to refine them to measure circuit activity in humans. There are things like functional MRI which can see activity or can see blood flow changes in the brain that are related to activity. And we have experiments going on in patients who require deep brain stimulators or electrical recordings to be made inside their brain to record neural activity from the human brain itself. There is still a large gap however between the deep knowledge we can get at the animal level, and the less rich data we can get at the human level. But that is clearly the challenge to bring these two efforts together, this kind of deep understanding of circuit activity that we can get from inside the brain and animal models and the circuit activity that we can measure non-invasively or in some cases in patients who have deep brain stimulators, or electrical recordings.

G: We've talked about cataloguing the cell types of the brain and we've talked about observing them in action. The final piece is really to be able to modulate activity in those cell types so that one can reverse deficits that are seen in illness. In mice, we have a plethora of tools to be able to turn on neurons, turn off neurons, regulate their biochemistry and not just do it in bulk, not just do it in a large chunk of brain, but actually do it in very, very specific cell types. Those experiments have shown that you can get exquisite control over behavior by exquisitely controlling the activity of these neurons. The challenge is to be able to move that in the direction of being able to operate in human beings. We already have some tools that can affect neural activity in human beings that are used today. Deep brain stimulation, Walter mentioned, is where an electrode is placed through the skull deep into the brain and you can stimulate a small chunk of tissue around the tip of that electrode. We'd like to be able to and brain projects are trying to figure out how we can direct that energy, direct that stimulation to evermore specific components of the neural circuit. We also have external means noninvasive ways of stimulating the brain and that includes magnetic stimulation, that includes externally applied electrical stimulation. And what's really new and has really blossomed with the BRAIN Initiative is ultrasound stimulation. These and hopefully other technologies give us the promise, I should say, to be able to control neural circuits. And what we need to do is combine the technologies of observation so that we can figure out what specific cell types we need to manipulate with advanced stimulation technology to be able to do so in the human. And I would say that it's important to remember the goal of the of the BRAIN Initiative, in this respect, the goal of the BRAIN Initiative’s to develop these technologies in the service of repairing unseen damage, if you will, repairing the brain, rewiring the brain in cases of illness so that we can restore full functions, so that we can enable recovery. People are suffering from neurologic and psychiatric disorders.

K: In the future, I think what we see is a whole new way of interacting with the brain to promote health and that is going to be precision ability to modulate and monitor neural circuits in the brain. And this will give us the ability to say, look at the patient with chronic pain and try and understand exactly where that pain signal is coming from and turn it off when it is not a valuable to the function of the human. The BRAIN Initiative I think the promise is almost infinite in terms of understanding brain activity, understanding how our brains work, how we think, how we communicate, our emotions but the focus at the NIH level is clearly on providing benefit to those people who are suffering with neurological, psychiatric and substance abuse disorders. Thanks very much.