We'll talk about future directions in brain stimulation. So this is a kind of fun talk just at the end and please feel free, just raise your hand and interrupt me if you have a question, you know don't mind at all.

So I want to talk about a couple of things that Dr. Homayoun brought up and this is going to really show you the whole spectrum of kind of what is easier to do but still difficult that would be new in DBS and then kind of what is very futuristic. So there is a problem with primary freezing of gait in Parkinson's disease and maybe also as its own entity and for this specific problem simulation of the pedunculopontine nucleus has been you know suggested and tested in patients and the pedunculopontine nucleus is one of the outflow targets of the basal ganglia, it's lower down in the brain in an area called the locomotor region, brain stem locomotor region, and has direct outputs to the spinal cord. It also does have projections back up into the striatum. And it's been stimulated just one side, it's been stimulated on both sides, it's been stimulated with STN, it's been stimulated with GPi, it's been stimulated with this region above the STN called the zona incerta. And the long and short of it is that this hasn't happened in a controlled fashion and we are still not sure how well it works, but it's definitely worked well enough in some patients that it's an option. But this kind of highlights one of these things that is just kind of outside of our reach right now for instance in how to expand you know indications in movement disorder surgery, how to treat some of the effects that aren't well treated by our standard targets in movement disorders. And it's really only from kind of the larger academic centers that can receive these referrals and receive enough over time and to really study this in a systemic way and think carefully about this in terms of applying new targets in doing dual target stimulation that we can start to get some answers for this.

Okay, so in terms of targets and indications if you go to clinicaltrials.gov and you look up DBS trials you'll find that they are ongoing and by the way you don't have to be in the United States to list your study on clinicaltrials.gov, so this is kind of the worldwide experience right now. There is a one to one trial in addiction, there are - is a one to one trial on Alzheimer's disease, anorexia, bipolar disorder as has been mentioned, depression, epilepsy, OCD, post-combat PTSD, schizophrenia, Tourette's. So if you can think about it chances are someone else is already thinking about it for DBS and a lot of these indications are currently under investigation.

This is a good table by one of the longstanding English groups doing DBS so these are just the targets that have been used for Tourette's, OCD and depression and you can see the list is very long. In a lot of cases they overlap. But it speaks to one of the slides that was presented earlier in terms of functional basal ganglia thalamocortical loops and how these nodes are functioning abnormally in different disorders that have overlapping symptoms. /And one thing that's very - let me just I'll get there in a second, I don't want to forget that - in terms of thinking of targets one thing I did mention is that kind of in contrast to what the history of movement disorders where we are targeting gray matter structures and the subcortical structures the efficacy in OCD seems to in a large part be related to stimulation of the internal limb of the internal capsule which sits right above the nucleus accumbens which is also known as the ventral striatum. So if you can think of an MRI where you are used to seeing the caudate and let's say a coronal view the caudate and the putamen separated by the capsule if you go down deep enough they actually meet. So that's the ventral striatum also

known as the nucleus accumbens and right above that is the internal capsule. And so the electrode is actually in the anterior limb.

The group at Emory and Toronto in conjunction with a very good imager at Case Western have - are really leading the field in terms of looking at white matter tractography, so these are anatomic studies that I have to tell you are really subjective, so if you see publications or you see pictures of tractography and it looks very pretty these are really subjective. But this group has done some very nice work with DTI tractography and looking at areas of activation, so there are models that can estimate how much tissue is activated by a different current delivered in different electrode combinations and they basically have shown a difference between, between responders over here and nonresponders here. Actually this was a contact in which the patient reported you know a clear benefit in terms of symptoms, this is a depression patient, and this was a contact where this was the estimated tractography was affected. And here this was the estimated tractography.

So you can see here where you are affecting more of the network you know the overall loop, and here you are just not making it there. So one of the reasons why the most recent depression trial probably failed is that some people's you know electrodes were creating a picture of stimulation like this and other people were like this. And that's one of the issues is that when trials go to these large multicenter trials before we understand things like this they are likely to fail and it's actually a real problem in the field now because these are expensive trials and if industry doesn't fund them it's a question of how are they going to get funded. And so these are going to have to be funding kind of at individual institution level with a number of different kind of creative mechanisms for doing that.

Okay, Dr. Popescu mentioned this idea of closed loop stimulation and actually I didn't really go into this further or earlier in contrast to open loop stimulation, or open stimulation. So that you know we set the device in our movement disorder patients and it's on and it goes. And then that has an effect over time and then there may be side effects or other adjustments need to be made for improving efficacy and we modulate that, we you know turn it up or we do some kind of experimentation in the clinic with the patient. But then when they leave they have a setting and that's the setting. And then maybe with the patient programmer they have a B setting too, so in some people maybe they can make a little switch or they can go up and down.

But what the RNS system does as has been mentioned is record all the time and then deliver stimulation based on instructions that are given by a clinician through a programmer. But that can be modulated. Now that still requires recording analysis and modulation by the clinician. Eventually these devices are going to have the ability to learn and that is going to require instruction but machine learning is eventually going to play a role in these devices such that they can learn different patterns and modulate their activity based on dynamically. Of course in response to programming by humans.

And I think this is what the future looks like for closed stimulation. So we have very crude electrodes now in both the systems that have been talked about today, and you know these are very large contacts and they stimulate large populations of neurons and actually this slide is really out of order. So Dr. Homayoun mentioned this idea of current steering so here are current electrodes and

you get a big sphere and you can kind of stretch this sphere a little bit you know if you turn this one on or maybe you can turn on two of these, or you can kind of change how they stimulate but you can't do a whole lot with this. You could create the same sphere of activation with a bunch of electrodes but you could also shape the charge distribution and you could think about fitting it within your structure of - your desired structure whether it's a gray matter structure or a white matter structure. So this idea is called current steering, you can think of it as shaping the area that's affected by DBS.

Let me just go up here again and show you why I put this on here. These are microelectrodes. Someone asked before about you know what's the difference between these recording electrodes and the stimulating electrodes, so you can see here is a microwire bundle, so these would be very thin, I mean a hair - less than hair thin microwires that would extend into the brain and these can kind of go in a bundle. They can come off in a ray that would sit on the cortex and have like 100 penetrating electrodes and these have been used in brain computer interfaces for instance in patients that are paralyzed from spinal cord injury in order to control the prosthetic devices. And these are actively under development and one of the - just looking at the clock here - this I'm showing you this paper because it really, it wasn't the only paper but it was - it's a kind of well known paper that kind of has moved the field forward in a number of ways. So in patients that underwent intracranial monitoring in order to detect a seizure focus this group at UCLA did some stimulation studies specifically related to memory function. And they reported and there may be a follow-up paper that says something similar but still I think they are really the only ones that have shown the kind of strong affect that they did and improvement essentially in memory function. And this is very interesting

and it's interesting related to the RNS device because it may be even if we can't stop seizures that we can somehow shift the network dynamics to affect cognition patients so that someone who is having epilepsy isn't affected as much by their seizures, or by a baseline network dysfunction that number one predisposes them to seizures, and number two is responsible for cognitive impairment.

So in light of this, the Defense Advance Research Projects Agency, also known as DARPA, just awarded about $80 million for these two projects, primarily to just 4 institutions working on conjunction with NeuroPace is one company, Medtronic is another and some of the other device firms that are working on micro stimulation. And I tell you that because this is, so this is part of the Brain Initiative. You know it's interesting, this is kind of an aside then we are running out of time. But you know Obama said well we are going to have $100 million for brain research which is basically nothing you know going into this NIH. But DARPA which has a different kind of funding mechanism just gave you know 80 million bucks away to several different places.

But just I want you to read these if you don't mind if you don't like reading slides, but number one is called restoring active memory and so the point is to develop and test a wireless fully implantable interface that's a neuroprosthetic and the idea is to improve someone's ability to encode new memories or retrieve old ones. Okay, no one knows how to do this, not even close. However the point is there is going to be a lot of exciting stuff happening in this field and it's driven by some of the work in our epilepsy patients that have implanted electrodes and we have ongoing studies in our own epilepsy monitoring unit, it's also driven by data we can collect when patients are awake in the operating room undergoing DBS and we have studies related to that as well.

Here is the other one, the SUBNETS, reduce the severity of neuropsychological illness of course in service members, veterans, basically with the same type of technology, sensing enabled technology that detects biomarkers for instance of depression or of anxiety or of posttraumatic stress disorder and then stimulates desired brain regions. And the group at MGH was involved in one of these studies and this is the schematic of what this would look like and it's similar to the picture I showed you before. There are different types of electrodes, they are implanted in different parts of the brain and there is an interface and you know very smart computer system essentially that is going to modulate the detection and stimulation.

So I really do think that's the future of brain stimulation. It's going to take us a while to get there but these things are popping up in the news now, so just to give you an idea we are very, very far away from even doing these in patients because a lot of this funding is going to go to device development. The devices to do just some of the general ideas that have been proposed literally do not exist so they have to be developed.

Okay, so in conclusion, this is really kind of conclusions from the course, DBS is the gold standard of treatment for Parkinson's, essential tremor and primary dystonia when symptoms are not controlled with medical management and when patients otherwise meet surgical criteria. And there are multiple efforts underway to expand what we've learned in movement disorders in terms of brain stimulation to other circuit diseases of the brain, and we've kind of given you an overview of that today.