So I'm gong to talk briefly about use of deep brain stimulation in Parkinson's disease and I'm going to cover more of the scientific background, some of the efficacy data and then my colleague Dr. Berman is going to talk about the practical aspect of patient selection.

So I'm going to talk about the targets we use, mechanisms of action, efficacy and a very brief discussion of what would be next. So the size of the - probe of the DBS which we put in the brain and where it's located that gets the name of deep brain simulation, it's basically a revolutionary type of treatment. If you think about the ability to modulate the activity of the brain really for the first time to get clinical results, and I think you know as we talk about the mechanisms and our understanding this - you know the idea I think from a neurological perspective is this is still a kind of a crude technology despite all we can achieve with it. And if we an fine tine it we probably can do better.

So as Mark talked about this we are talking about this idea of the circuits, the loops between cortex, basal ganglia and thalamus. And these parallel loops as far as it goes with the motor cortex, motor system they go through these loops the information that is required for performance of motor actions. The role of basal ganglia is thought to be more of a modulatory role, fine tuning of movements, certain aspects like scaling of movements, sequencing initiation and the type of thing we see affected in diseases. There is a parallel processing and there is also a topographical organization which is very important which part of the body is affected and how the system works.

So the idea of these parallel loops as was mentioned, the other parts including ocular motor, reward or limbic system which involves the cingulate cortex or the prefrontal cortex, the prefrontal or called associative or executive loops and these loops work in parallel. All of them share this pattern and the ability to stimulate one circuit separate from the other ones allows us to make a modulation without affecting those other functions.

Now going a little bit into what was the contribution from Dr. Delong, which was mentioned, and his colleagues in terms of this box circuit idea of basal ganglia which still kind of derives our major way of thinking, so the initial you know model would indicate you know we have the cortex sending signals to the striatum, that's where the dopamine is working. And we have a different role between D1 and D2 receptors. The direct pathways which go to the output of the basal ganglia, GPi and then send the signals out to thalamus, back to cortex. When we think about the direct pathway mostly as let go for a motor to be exerted and an indirect pathway which involves the subthalamic nucleus and as a final outcome it's like a brake on the movement. Now in reality the circuit has become much more complicated but still we think about these two main ideas of let the movement go and stop is holding true. One of the key features that we now think about is this pathway form cortex to subthalamic nucleus which is now called a hyper-direct pathway and is a direct excitation through the indirect pathway. We can think about a way for our cortical control to stop an unwanted movement and there seems to be some of the possible involvement of how DBS works may go to that hyper-direct pathway.

So what happens in Parkinson's is substantially nigral neurons degenerate, we have a lack of dopamine in the striatum and therefore this normal dynamic is supposed to change. So the change happens in the direction of weakening the direct pathway, strengthening the inhibitory in direct pathways and that is thought to be translating into more difficulty with initiation and exertion of movement, the slowness that we see in classic Parkinsonism. And what we think about why the levodopa is helpful is because it allows the brain to make the dopamine or allows the dopamine act on the striatum in the case of dopamine agonists and we were able to reverse some of the motor deficits of Parkinsonism. So the idea of DBS is are we able to change anywhere else in this pathway with you know electrical stimulation to replicate the effect that we can pharmacologically see from dopamine and we know we can do that.

Now how can we do that with putting the electrodes in a specific part of the brain to get to that result? Again, now we think it's because we really are going to modulate the circuit. The initial idea came from you know observation that when they were using the stimulation in operating rooms to do lesioning and for which was you know kind of established treatment for some of the movement disorders, a high frequency stimulation could replicate and effect of an ablation. So as a thought about you know deep brain stimulation primarily have an ablative or functional lesioning in that part of the brain, but you know the benefit of being reversible, you turn the switch off and then the lesion goes away. Now why you know this was the basic idea of how it works. In reality we do recordings from subthalamic nucleus during this period of stimulation some of these neurons stop firing, but there are some other neurons in this area that increase their firing, that don't change their

firing. So it's a more complex picture and that kind of drove the thinking that it's not just the rate of firing of neurons, there's more into it.

So what happens when the deep brain stimulation is affecting, you know sending the electricity towards a neuronal environment around the tip of this electrode, so we have the neurons. We think the primary effect on the soma of the neurons, the body of the neurons which are close to the electrode is an inhibition but the pathways, the axons that are leaving could be excited primarily and then they have affects on other components. They can also have an effect of stimulation on adjacent or passing by tract fibers. And now we think that's also a part of why it works. It's not just the subthalamic nucleus, some of it is just the fibers that move next to subthalamic nucleus.

And now what is he evidence that we are doing more than modulating the rate? Now we know for example that when we use the DBS the pattern of firing of neurons changes, so here is high frequency stimulation of subthalamic nucleus recording from GPi neurons, they become very rhythmic. The same thing happens in thalamus, they become rhythmic. So with high frequency stimulation we basically change the pattern of firing of the neurons so it's not just changing the rate of their firing. And the bigger idea is we try to normalize the abnormal pattern of activity in this part of the brain.

And a step forward in terms of what we think about it these days, this idea of oscillatory activity that Mark referred to, so we have now evidence that there is abnormal oscillatory activity in key output areas of basal ganglia as well as in subthalamic nucleus in Parkinson's disease, which we don't see in

other subjects. And these are based on direct recording from patients with PD. And one of the ideas here is we have the neurons that are firing, the recordings from local (inaudible) potentials and there is an oscillatory activity which this firing of neurons are locked to that. We can see there is a peak of frequency that usually falls in the beta range, and that's why this is called the beta band oscillatory activity. And now this has been shown in a number of studies. So it's the recordings from individual patients with Parkinson's you see they have a peak of beta activity. Some of them interestingly may have two peaks of beta and this is not - this is a fixed frequency for each patient but it's not the same in all the patients. So it's very individualized. And in some of the recordings that are 2 recordings from bilateral sides they are synchronized to each other. So these patients carry an abnormal hyper oscillatory activity in the beta band frequency and now there is evidence that it also is related to their abnormal movements and ability to move fluently.

So some of these works come from comparison here between the on and off state with the medication. The red line is during the off state when there is no medication and the beta frequency is there. With an on state where their symptoms improve the beta frequency is suppressed. In fact there is some higher frequency in the gamma range that become active in some studies, but this is the most consistent. So the idea is you have some frequencies that are anti-kinetic, the beta frequency between cortex and basal ganglia, and then some pro-kinetic frequency. And this is one of the key things that we are trying to treat. There is also an idea that tremor frequency which is not present in all patients is also very individualized is another type of oscillatory activity. So this beta frequency is more timed to bradykinesia, the core motor deficit, the tremor frequency individualized in patients who have tremor and we know DBS treats well for this and so the idea is that it disrupts that

oscillatory activity, and that's how it normalizes the activity in the system. So there is some evidence clearly that - this is again recording patients with Parkinson's, there is a difference when they perform a task if go or no go, so the difference is for a task to be exerted they need to really suppress the beta oscillation or beta synchrony, and there is less suppression when they don't do it. So basically you need to suppress your beta synchrony to exert the task. This is whether it is a stimulus induced task, it correlates with reaction times, the earlier you suppress the beta, the earlier you do the reaction time its activities in the beta range that changes on levodopa becomes a faster high frequency but you don't see that beta frequency on the spectrum, you see the beta suppressed, you may get some on the gamma range. And this suppression clinically interestingly correlates with the motor improvement, I think it's one of the more convincing evidence that it's causative here. Another example that on a self paced movement in patients with Parkinson's this deep dark blue area is the area of beta synchrony, beta oscillatory activity. It gets suppressed when they are on levodopa, you get some of this you can call it a good or prokinetic oscillation but this anti-kinetic oscillation goes away.

And now what happens with DBS? Now recordings from patients in operating rooms recording this beta synchrony when the DBS is working and then they turn it off after a longer period of stimulation like a 5 minute stimulation and for a period of time, up to a minute, you still have this suppression of beta synchrony. It's kind of time dependent. If you do like a shorter period you get a little, and then it goes away. And that's during the period that they still have the benefit even when the system is off and then the benefit goes away. So now we have direct evidence that the same thing that levodopa does the DBS can do in terms of changing the synchrony. So this seems to be

one of the key functions of how it works. And also brings the door open to the idea of okay if we can tap into this abnormal synchrony in an individualized way, because it's different for each patient, maybe we will have a better way of controlling symptoms if we can you know promote the DBS technology to the next generation.

Now on top of it we talked about the network and we know these changes affect the whole network. So the whole idea of these targets which we us STN and GPi as a standard target are that they are working but the idea is if you can tap into this network in any other place that you get the same result without interfering with the normal function you should be able to get the same results because it's a network effect. So some way of looking into it which has been the idea that we have this resting state activity which you can look with FMRI, and this is abnormal in patients with Parkinson's disease. So there is some now evidence that in patients with Parkinson's disease there is a change in the coupling between these areas in terms of how the two areas connect to each other. Maybe shown better here. So it's thought to be an end result of when we put electrode in STN we exert a modulatory activity on a number of areas in this network, there is a positive modulation of thalamocortical pathway allows the movement to happen. There is also some inhibition of this hyper direct pathway which is kind of decreasing the activity of subthalamic nucleus so - and that's partly because of these adjacent fiber tracts which go through it. I think that's part of the reason why it works.

And finally in terms of how DBS works, keep in mind that there is - if you turn the DBS device on and off you have some immediate benefits which go away. Like tremor for example appears right

away, but there are some effects of the DBS which may last for minutes or even in hours. So some of the rigidity and some of the axial benefits may take hours to wear off. So we know there are different types of mechanisms, it's not just a single mechanism that delivers the effect of DBS because these symptoms wear off at different pace. Then we have some other conditions not Parkinson's but most notably dystonia that we have a much more delayed way of acting of DBS in patients with dystonia turning on and off the device doesn't do anything. They have to be adjusted and be on those settings for months at least to get the benefits. So then we think it's some affecting of the same network but to a mechanism that involves neuroplasticity. So arguably there may be some of this involving Parkinson's as well, but in terms of motor symptoms we think about the shorter period of time.

Now what's the evidence for clinical efficacy geared to our brief summary of - now we know this is working and you know that's why we are clinically using it. It's an aggregate of some of the major studies with Parkinson's showing the percentage just for you know improvement in major parameters. So motor score during the worst time off medication there is improvement in that; motor score during the best on time even gets better. Activities of daily living give more of a quality measure off time which is decreased in off time, the dyskinesia gets better and they are able to cut back on meds. So like major factors that we would consider as an indication for Parkinson's disease, there are multiple major studies that confirm the efficacy. And there is a list of those.

The big idea, the more common situation we would use it is this idea of the patients to get into fluctuations. They have benefit from levodopa and then they fluctuate. They have periods of time

that they may very low on their dopamine level and as a result they lose that benefit of levodopa, it's a turn off, and then there we have this peaks that are associated with abnormal involuntary movements which usually develop after a few years as a result of sensitization of the (inaudible) receptors and other mechanisms. So these patients the goal for us is to decrease the dyskinesia and to decrease this off time and that's what it tries to do, to give them more a stable baseline, the medication still gives some benefit but even if there is no medication there is a much better baseline compared to when the device is off. And that's you know that's the way we look at this.

Now again this was like one of the major earlier studies, the different stimulation study group that showed we can achieve a better improvement of on time without dyskinesia when we use the EBS. Another major study was when directly comparing the DBS effect to the best medical therapy and again the major change was that you may get with DBS an improvement in the mobile time without dyskinesia. So you can improve the good on time and you know in some of the studies this translates to maybe 4 or 4 1/2 hours of better on time a day, which makes a significant difference for patients. And there is also evidence that this directly correlates to the quality of life because that's the big message here of when we consider DBS.

Now there is a more recent study and it's kind of a comparison. The patients who underwent DBS at a more advanced level, and patients who understand at an early level. This is kind of a new you know incentive that is driven again by Europeans and they said okay we start to implant a DBS early in the process when they still can be managed well with mediations, does it going to happen to help with the quality of life? And it was, I mean there is an improvement when you turn the DBS system

on whether they are more advanced or even in the early phase you would get an improvement, in this case as kind of a Hoehn and Yahr Stage which is a measure of their mobility and there is also the same improvements in the quality of life measures.

Now there is also the comparisons, there is like big studies that was done, one of them was a VA initiative, and a couple of previous ones to compare the two targets we have, STN and GPi and basically I mean there is not a huge difference in terms of their motor efficacy so we kind of consider them equivalent, the big difference is in terms of if there is side effects, for example that one may deal better with, the ability to cut back on medication maybe a little superior. So the motor benefits are very comparable going back to the same idea that we are modulating the network so whether you do it at STN or at the output point of GPi you get the same results.

In terms of the ability to cut back on medications STN has been doing better and that also can be kind of consistent in most of the studies I would say. This is a cartoon in terms of overall they are maybe considered a draw. We tend to use STN a little bit more and it's like a little bit more in a smaller area, easier to manage. One of the you know advantages is in terms of ability to reduce medication, STN is superior. In certain patients for dyskinesia suppression GPi may be better although we a lot of times can do it here as well. There is also this concern that sometimes when there is significant problems with psychiatry issues or cognitive issues or very severe speech problems there may be some advantage to place it in the GPi, once again it goes to the discussion of patient selections.

And finally and very briefly talking about what's next. So we basically use these electrodes that Mark showed to chose how to do the stimulation. Now there is a field of stimulation, that's the area where we deliver the electricity and that's where we would get the results from. We can change this field of stimulation by choosing you know where we do the stimulation. If it's a larger field or we use a higher voltage we can get the bigger field of activation. We can change that pulse with duration of the pulse with stimulation, that translates into the neural elements that are involved so if you get the same area of stimulation you may partially involve the elements or you may completely involve the elements and get a different type of results.

Now why do we want a bigger field of stimulation? To get you know stronger results but why do we want to limit it? To prevent the side effects because when the electricity goes to the adjacent areas we would get to the side effects, the tingling, to the sensory pathways, pooling or weakness or dysarthria when we get to the internal capsule pathways, so we want to keep it focused.

Now we have limitations with current technologies and you know thus again why we get the problem because in STN we try to be in the dorsal STN and you are not close to the internal capsule pathways where we get most contractions and so forth, so ideal is we stimulate the area we want and avoid the area we don't want but remember here with our current technology we have a circular like a round shaped field of stimulation. So one of the you know ideas if you can change the shape of this, because we don't go send electricity in all directions, so how can we do that? A big idea here is what is called current steering. This is our current type of electrodes and this is what is you know the next level of the electrodes, have a more number of smaller electrodes and the idea is then you

are going to be able to send the stimulation in a directed way so this is what we get. You have to put at the center, the red area is the area of stimulation and if you get here and you go outside you are going to get side effects, but if you have the ability to do the steering with this more advanced type of electrodes we will be able to get stimulation in the area we want and avoid the area we don't want. And this is really one of the most important practical problems we have when we do the programming. So I think that's one of the things that makes the programming harder because even with 4 contacts it's very difficult to do programming, have a lot of parameters. Now imagine you have a lot more to do, but it's going to give you a lot more ability to do. So it's an interesting challenge. And these thing have been already made, been already showing efficacy in small. They are not ready yet for primetime, but this technology is kind of very close. And this is again the idea, instead of going through the whole round area you define where you want to do the stimulation to kind of you know custom make it, and that really would be interesting.

The other idea in terms of what we do is this idea for closed loop, we talk about this responsive neurostimulation, the idea is you get the signal from the brain, give it back to it. So just briefly and Dr. Richardson is going to mention that too, I mentioned this oscillatory activity and you know one of the signals now we say this beta band synchrony is an abnormal signal and it's kind of individual as to the patients. How if we can record this signal in real time to the electrode in the brain and then disrupt it when it comes, and maybe even disrupted in a frequency specific way. So that's what the idea of a closed loop circuit targeting and signal that you know is abnormal. And we are learning more about the brain and what are the nature of these abnormal signals in the brain which a lot of them in the psychiatric disorders we may be able to this I think would I think a huge applicability.

You know this is again some major studies were published in the primaries, the system, the ability of doing this already exists and the ideas is you can basically pickup the abnormal signal or you can pickup you know the feedback signal from the cortex and deliver the signal to the basal ganglia and get an improvement in the experimental Parkinsonism.

So pedunculopontine nucleus has been suggested as an area that is involved in axial control of gait, it has a cholinergic component to them. We know it's one of the things that in Parkinson's it's not under well control is the problem with freezing of gait and aspects of the you know fluidity of gait that is not levodopa responsive and there are some preliminary you know data to suggest with the DBS in this area that can improve freezing of gait that is not responding to levodopa. It's a very deep area in the brain so Dr. Richardson should go really deep there, but I mean it's apparently feasible to do, especially with MRI guidance.

And another idea of this kind of abnormal oscillatory signal which I think is an interesting study was they for the first time in the patients who have Parkinson's they put these electrodes that do the recording. They recorded patients when they have walking and they have freezing of gait. This is really interesting data, we don't have a lot like that. And what we saw is there is an oscillatory activity that correlates with the freezing of gait in these patients, and that was interestingly in the alpha band, not in the beta band. And it was in a specific part of PPN, this was more a caudal part of the PPN that this signal was there. And they then did the stimulation, this was a small case series that could improve the freezing of gait in these patients and the best results were gained where they

did the stimulation at the area that had the highest alpha frequency. So to kind of break this alpha oscillatory activity that correlates with the gait.

Now there is a caveat here, all of the talk is about high frequency signal which we think about to disrupt the activity, and in this case the idea with the alpha synchrony was it was actually something which was beneficial to gait, if they had the alpha they were doing better. And it is a low frequency signal, which we usually think is stimulatory. So this is very primitive of course and that's it for now.