As Dr. Richardson said my name is Bob Hudak and I'm the Medical Director of the OCD-IOP and I want to go over today some of the research that is behind OCD and deep brain stimulation.

Okay, so first off today I want to give you some background about OCD and how we came to use DBS in OCD. First off OCD is a little bit of an interesting diagnosis in psychiatry in that it's a dimensional and not a categorical diagnosis. And by that I mean that most of the diagnoses we make in psychiatry are categorical such as major depression, most people here know that to meet the criteria for that you have to meet 5 out of 9 criteria. You know you have 9 symptoms and once you meet 5 you have a diagnosis.

Now OCD is not that way, OCD is a dimensional category, which means that basically we sit and interview you and decide you either have it or you don't. And you are somewhere along that dimension. And as a result on one hand it makes OCD one of the easiest diagnoses to make in psychiatry because you simply have to have either obsessions or compulsions, and that's it. And if you have obsessions or compulsions and they are recognized by the patient as excessive and if they cause some marked distress with the person you are diagnosed with OCD and that's pretty much it.

DSM-IV and DSM-5, by the way DSM-III did not do this, but DSM-IV and 5 does say you can have either obsessions or compulsions, I will tell you that in clinical practice virtually everybody has either - has both obsessions and compulsions I should say. I don't know that I've ever seen anybody that's had obsessions only without compulsions or compulsions only with obsessions. There are a large group of patients on the internet, they talk about having pure obsessions, they call themselves

pure O, they are kind of an internet subcategory of people. I've seen many people who have considered themselves to be pure O and again they almost always have compulsions associated with their obsessions.

Okay, so what is an obsession? And while OCD is technically an easy diagnosis to make it's confusing for a lot of medical professionals and even - excuse me, and for a lot of mental health professionals because of language issues actually and you know what is an obsession. I have a lot of pet peeves, I have a current list going, I think I'm up to 528. I added a new one in the last 2 weeks, so I was at 527, I'm at 528 now. If you've been watching ESPN at all over the last 2 to 3 weeks they've been talking about football being the national obsession. What they say is well if baseball is the national pass time football is the national obsession. That just sets my teeth on edge because of course football is not an obsession, it's not a national obsession. It may be a national preoccupation or a national fixation, but an obsession it is not. So an obsession is very different than a preoccupation or a fixation because obsessions are recurrent and persistent unwanted thoughts, urges or images that are inappropriate. So what is an obsession, obsession is something that actually people don't like. It's a thought that makes them feel very uncomfortable. So by definition football would never be an obsession because people like watching football.

Sometimes people mix up obsessions and addictions or compulsions and addictions because they think that the need to use a drug over and over again is a compulsion. It is not a compulsion because again there is nothing recurrent or persistent unwanted, there is no unwanted nature about that thought. So that's just a brief what an obsession is and the obsession is not a worry that the person

has, so the obsession is different than an average worry. So if you worry about something all the time that's very different than what an obsession is. And this actually comes into play later on when I show you some functional MRI research that's been done. Obsessions feel as if they are imposed on from without, they almost feel alien in some way, but the person recognizes it's coming from their own mind and there is always an attempt to try and suppress the thought in some way.

So a compulsion is just simply the repetitive behavior, a mental act that the person must perform. So when a person gets an obsession they attempt to suppress that obsession in some way, and the way it's suppressed is with a compulsion. And it's important to note that the compulsion and the obsession do not always match each other. So for example someone may have an obsession about germs and may think that their hands are not clean. And most of you here might say okay well then their compulsion must be that they are going to wash their hands, and that's not always the case. Their compulsion may be if they feel their hands are dirty that they will pray the germs away off their hand, perhaps they'll chant, they'll just there and say I am clean, I am clean, I am clean to get rid of the germs, okay. So the compulsion and the obsession do not always match. And in the short term the compulsion makes them feel better, of course the catch is that the compulsion always comes back and it comes back even worse. The obsession comes back even worse, I'm sorry.

So OCD was originally thought to be a very rare diagnosis, now we know it affects about 1 in 40 people and it's equally common in adult males as it is in adult females. It's a little more common in the pediatric population in males actually, but by the time they get to adulthood the rates are normal

and that's one way that OCD is very different than any other, than other psychiatric disorders is that most psychiatric disorders seem to favor females, this one is equal.

One of the important things about OCD is that even with adequate medication and cognitive behavioral treatment many patients are treatment resistant and the treatment resistance rate in OCD is incredibly high. We don't have a real consistent definition of what treatment resistance is in OCD unfortunately, but depending on how you want to calculate it maybe 40% of people with OCD do not respond to convention treatments. So what do we do at that point? We need to do something additional and some very aggressive treatments are often needed. This can be a very debilitating illness and it's one of the most debilitating conditions in the world. The World Health Organization actually ranks OCD as one of the top 10 to 20 reasons for chronic disability in the world, and that's not psychiatric disability, that's all medical disability. So again this is a very severe illness.

Just to give you an idea of what the typical flow chart would do, a typical algorithm for treatment. What we do with people with OCD if they are mild we usually give them cognitive behavioral therapy, we don't even bother with medications with mild people. If they are more moderate to severe we try SSRIs. And as I said a number of people, maybe up to 40% of people, will not get a response and what we do is we put them on a second SSRI. We will switch one for another. If that doesn't work what we consider is augmentation with Clomipramine, and if Clomipramine does not work we'll try to go fully with Clomipramine, we will take them off the SSRIs altogether and use only Clomipramine. And then again if none of this works we consider augmentation, and with augmentation we have medications like antipsychotics or Memantine, which is also known by the

trade name of Namenda. It doesn't work real well with dementia which is what it's approved for but works much better for OCD than it does for dementia. And again if that doesn't work we consider trying different antipsychotics. There are other medications to try such as Ondansetron which is an antinausea medication called Zofran. And again if there is no response to that there is other agents we try as well. There is other second line agents, second line antipsychotics, there is a whole raft of other antipsychotics and treatments that we may try.. Suppose all of this is tried and none of this works what do we do? Well then we go to treatment refractory patients and then we try the more experimental treatments such as neurosurgery at that point.

Now once upon a time there was a secret cabal of psychiatrists and neurologists and they all got together in a room somewhere and they said okay just kind of arbitrarily said psychiatrists you take these illnesses, and neurologists you take these illnesses over here and we'll pretend like they are completely different. As someone said in the back earlier in the morning session talked about depression having an organic cause and we know that many of these psychiatric illnesses do have a medical cause to them. And what is important about OCD is that OCD probably has the most well defined neurological basis of all the psychiatric illnesses. And I think if that secret cabal of psychiatrists were to meet again today neurologists could actually make a good case that no, we are going to take OCD away from all of you shrinks here and we are going to treat it ourselves because this is really a neurological condition.

So there are some implicated regions in OCD, we have the orbitofrontal cortex, the anterior cingulate cortex and the caudate nucleus. There have been neutral state studies, hyperactivity at baseline. So

in other words you put someone with OCD in a PET scan or an FMRI scanner and these areas of the brain right here are more active than they are with someone without OCD at rest. And what they've done is pre and post-treatment studies, they are attenuated with treatment. So in other words when you treat someone with OCD the hyperactivity in these areas goes away. This actually was a big deal. I was a resident when the studies were first published in UCLA that showed that therapy and I mean cognitive behavioral therapy had the same neurochemical changes that SSRIs did in the brain. And that was a big deal at the time. That was the first time that anyone ever showed that therapy could do the same thing as medications in treating neurological biochemical changes.

And then later on what they followed this up with some symptom provocation studies and this is a little bit of some of the cruelty that researchers often have. My wife is a researcher so I don't like to make fun of them, but so what they did is - what they would take OCD patients and they would put them in the scanner, take a look at their brain and they'd say okay now we want you to worry about your marriage, worry about your job. And guess what, those regions of the brain don't light up. And then they would, and then they would try to symptom provoke their OCD and usually what they'd do is give them a dirty rag. So then they are in the MRI scanner and they throw in a dirty rag. One thing that will bother an OCD patient virtually more than anything else is a dirty rag. So give them a dirty rag and those areas of the brain light up. So just normal worry doesn't do it but an actual obsession does. And one of the nice things about these studies where people really acted as their own controls then at that point.

And so what areas of the brain were lighting up? Right here, see the orbitofrontal cortex and you know the caudate, thalamus, globus pallidus right here. So these and this was the - it's called the frontostriatal thalamo-frontal loop and this loop is the proposed circuit that is underlying OCD. I'm a little bit more of a schematic kind of guy so here this is in more anatomical but still schematic version, so the orbitofrontal cortex and then the thalamus and the caudate nucleus and what I'm most comfortable with is fully schematic drawings. Okay, so with this drawing here really illustrates is the loops that we hypothesize right now are affective with OCD and what the DBS target is.

So right her we have the orbitofrontal cortex and the thalamus and the striatum and what is really thought to be going on is that the cortical thalamic loop right here seems to be hyperactive in people with OCD and/or this loop right here between the orbitofrontal cortex, the striatum and the thalamus, this loop is underactive. And this is actually an inhibitory loop so when this loop here is active it damps down that part of the equation there. So you either have this is too hyperactive or this isn't active enough, maybe a little bit of both. And what the DPS target is, the DBS target is right here in this part of the loop to try and calm down the hyperactivity in this part of the brain.

Early on ablative limbic system surgeries were typically used for OCD in the most treatment resistant of cases. Okay, so what are the criteria? I'm going to go over the criteria for OCD neurosurgery and this includes both ablative surgery as well as DBS. So what we have to do before we do surgery with someone we have to do three adequate trials of SSRIs. One of the trials has to be of Clomipramine, you had to have tried augmentation with both an antipsychotic and a benzodiazepine. I think I know that I've gotten away form that, I don't consider that really to be a

criteria. I think it's still officially centers use it but there isn't any evidence to show that benzodiazepines do anything for augmentation. Augmentation with a glutamatergic agent such Namenda, and they also have to have an adequate trial of exposure with response prevention, that is the therapy that and the only therapy that's been scientifically shown evidence based to work for OCD. And they have to have a YBOCS of 28. The YBOCS is a scale to measure the severity of OCD, it goes from 0 to 40 and so you have to have a 28 or above, and that's considered to be a very severe level of OCD. Another statement to make about YBOCS is that people with the YBOCS it is not a - it's not a diagnostic study, it is something only used to measure the severity of OCD, so in other words it's not like - there is no minimum criteria for OCD to have a YBOCS. in other words if you have a YBOCS of 0 or 1 that doesn't mean you don't have OCD. That isn't the way it works. All right.

So I just wanted to briefly show you some of the targets that have been looked at for neurosurgery in OCD and ablative surgery. And anterior capsulotomy, that's right here, the anterior cingulotomy and the subcaudate tractotomy and these are three surgeries that have been. These surgeries were don either with thermo-capsulotomy where they put the electrode in the brain and essentially heat it up to kill the brain cells, or now what's commonly used is gamma knife surgery which involves radiation, they don't even need to cut the brain open. And again this is a more representational, the cingulotomy, capsulotomy and subcaudate tractotomy. One of the most common surgeries that is performed nowadays when they do do this is a surgery called the limbic leucotomy and the limbic leucotomy is just a cingulotomy plus a subcaudate tractotomy, and I have a neurosurgeon here in the front row looking at me if I get it wrong he's going to yell at me and I'm not seeing any dirty looks

on his face so I assume I got it right. And I just wanted to throw up some more pictures here, and these are pictures of what an MRI of the brain after you have an anterior cingulotomy. And this is the sagittal section. Okay.

So effectiveness of cingulotomy for OCD and they took a look at 44 patients and they had 32% responders and 14% partial. And the mean improvement in their YBOCS is 28% with minimal adverse effects. This was published in 2002. That mean improvement in YBOCS of 28% is important because if you figure that someone has a YBOCS let's say of 35, a 28% improvement is an improvement of maybe 8 to 10 points. At that point they still have a YBOCS of 15, 16, 17 so even with fairly robust improvement a YBOCS of 15, 16 or 17 is severe enough to land you as moderate OCD and enough to land you into most research studies. Just to let you know that even though these treatments work patients are still left with a fairly robust and clinical amount of illness. However it's interesting that people with OCD can often - will say that even with that 25 to 30% drop they really get a significant difference with their quality of life, they really can do a lot that they couldn't do before in spite of the fact that they sill have fairly significant levels of illness.

Okay, so I'm going to talk about some of the deep brain stimulation data. And this is just a nice picture I've thrown so people know what the - what it looks like. And I threw in this picture here as well which just shows you from pictures this is from the 2006 study which I'll be referring to and these are patients and these are what MRI - their MRI scans look like with the electrodes in place. And you don't need to be a radiologist to be able to determine hey here are the electrodes.

So deep brain stimulation for OCD was first used in 1999 and obviously I think that the reason for using it was because unlike ablative limbic surgery you can actually do DBS without killing brain cells and I think that's why it was originally tried. The original target was the anterior limb of the internal capsule and now they use the ventral capsule, ventral striatum. This was after a 2006 study which demonstrated greater improvements when they moved the site more posterior. So it's interesting in the review studies what they show is that one of the positive factors for improvement with OCD DBS is that you had your surgery later rather than earlier on in the case series because our siting is improved since then. There is a large multicenter trial underway that is double blind and includes sham control to determine the efficacy of DBS. And the trial is still ongoing and they are actually still recruiting patients at this point. And as I said here originally the anterior location was based on internal capsulotomy lesions and they started using more posterior sites and right now they are at the VCV, VC/VS.

So let me talk about one of the early studies. This was 10 subjects from Mass General Grown and the Cleveland Clinic Foundation. If you take a look at the original study my - I have a patient who is Cleveland Clinic No. 5 on the study. I still see him for follow-up every few months and he doesn't have a neurosurgeon, actually we'll contact you because he - we will need to meet with him together at some point. So they used the same inclusion criteria for - as for the cortical stimulation as the anterior cingulotomy. So this very, very strict criteria I talked about, they did the same thing for the DBS. They did all the ratings and they implanted the device and they do stimulation 2 weeks later. I'm not sure why the difference is for among the Parkinson's is what I heard earlier, but they do 2 weeks.

And here you take a look at the OCD severity. So the OCD severity dropped quite a bit after between 6 and 12 months of implantation. They got a really nice improvement with their YBOCS scores. So of the 10 patients they were able to follow-up 8 of them over a 36 month period and 6 of the 8 subjects experienced a 25% reduction in the YBOCS at 36 months, 4 of 8 a 35% reduction. That's a huge difference in improvement. Depression and anxiety improved at 3 months. We went over adverse effects earlier today so I did not include the medical adverse effects but some of the psychiatric adverse effects, people did have transient elevated mood. We got a nice description earlier of the super man syndrome, I really like that, but that's one of the side effects of this. And there is various bodily sensations and one person had an asymptomatic hemorrhage.

As I said my patient was one of these 8 patients here. Now he was one of the sickest ones in the study. I believe his YBOCS was a 39 and that's a 39 out of 40. Now his YBOCS nowadays is a 30, and that's a 30% improvement. And that's a dramatic improvement. A YBOCS of 30 however is still sick enough to be able to get you to be eligible for the study again. And that's how sick he remains at this point. But yet the difference in his life is tremendous. Before the surgery he was unable to leave the house or do virtually anything at all. He only would leave the house maybe once a month, and when he did leave the house it was, it was very difficult for him, he would try to get back in as quick as possible. Unfortunately one of the things he could not do in his house was use his bathroom. And so he couldn't leave the apartment, but at the same time he couldn't use the bathroom in the apartment. What he had to do was go in containers in the house. So he just had

containers filled with - because he wasn't able to do use the bathroom, not able to go into the shower. He would go for years at a time without being able to take a shower.

So I see this patient now, he leaves his apartment, he is able to get the energy to get out of the apartment 3 or 4 times a week. It takes him a couple of hours to get ready to leave. So he has to have the energy and that's why he can only leave a few days a week, it takes so much energy to leave the apartment he can't really muster that every day. But given 2 hours he can leave the apartment, he goes out and he goes shopping, he has some friends that he visits, some friends in the same apartment building. He's able to use his bathroom in his own apartment now, so he can use his bathroom and he does a shower occasionally. Now not very often but I do think he showers a few times a year now. So while this sounds like someone who is very impaired, and again he is, compared to how he was before the changes are dramatic, just absolutely dramatic.

And so this is from a recent metaanalysis, the average initial YBOCS of people given DBS is about 32, the YBOCS decreases about 8 1/2 points. Again this is a pretty significant improvement, they get improvements in GAF and HAM-D scores. Again the most common side effects are hypomania, that's that superman syndrome; anxiety; some paresthesias; dyskinesias; impulsivity; facial symmetry and some dysarthria, dysphagia and walking difficulties. And again interestingly later implantation seems to improve outcome.

So basically what you get is symptom reduction and functional improvement in about 2/3 of the patients. And like our Parkinson's patients who we were talking earlier, thank you all for that by the

way, they still have to take their medications. People who have DBS for OCD still need their medications, still need to do therapy. They still have clinically significant patients remain in most patients. Many of the side effects can be managed with the adjustments and depression worsens very quickly with stimulation interruption. So if you stop the stimulation they do get worse again, and they get worse again fairly quickly. Depression seems to get worse before the OCD gets worse.