[Carlos Belmonte]: Good evening to everybody. Could you please take your seats? Welcome to the session, William Safire Seminar on Neuroethics, Invading the Brain: What are the Ethical Issues on Invasive Treatments for Brain Disorders? I will ask to begin, the two institutions that have sponsored this session, to make a very short introduction of what are their objectives and their goals. Professor Colin Blakemore has the floor to speak about EDAB, the European Dana Alliance for the Brain.

[Colin Blakemore]: Thank you, Carlos. The European Dana Alliance for the Brain, for those of you who don’t know about it, is an alliance of over 200 European neuroscientists who have made a commitment to working publicly to raise awareness of the importance of neuroscience, both basic neuroscience and clinical neuroscience. It was established in 1997 and it is, in some ways, modeled on a parallel American
organization, the Dana Alliance for Brain Initiatives, which was sponsored by the Dana Foundation from New York. So the Dana Alliance in Europe, the European Dana Alliance for the Brain is very active and I think can claim responsibility for increasing the interest of neuroscientists around European communicating with their politicians and with the public about the importance of brain research, in particular during Brain Awareness Week, the week in March where there are activities all around Europe, and very exciting and innovative activities as well, and I know many people in the audience here have been involved in Brain Awareness Week events.

Why Neuroethics? Well, I think Carlos will tell us more in his introduction, but William Safire, the late William Safire, who was previously the Chairman of the Dana Foundation had a personal interest in bioethics. The Dana Foundation sponsored a meeting, a very important meeting in California ten years ago on the ethical implications of neuroscience and Bill Safire coined the word ‘neuroethics,’ well it had been used before, but certainly he was responsible for putting the word ‘neuroethics’ on the map, which has been enormously influential. So the Dana
Foundation through EDAB, has regularly now sponsored events to follow the growing influence of neuroethics at European events, so welcome.

[Carlos Belmonte]: Thank you very much. On behalf of the International Neuroethics Society, Dr. Helen Mayberg will now speak.

[Helen Mayberg]: Let me find a few slides. I’d like to speak on behalf of the International Neuroethics Society, as Colin said, really grew out of that first meeting in 2006, to be what is now an organization, the International Neuroethics Society, of over 300 members. And it really is an interdisciplinary group that really represents the essence of, I think, many of the people who are attending tonight, of people who really care about the social, legal, ethical and policy implications of the advances in neuroscience that are really the basis of what we’re all doing at the FENS meeting.

The mission is really to develop responsible applications of neuroscience through international and interdisciplinary discourse, and the organization itself has worked to sustain those interactions through the activities of its meeting. Everyone, on your seat, had to pick up a flyer which we brought
from the States to advertise the annual meeting which will be two
days before the Society for Neuroscience, this year in New
Orleans, and I think what, particularly young neuroscientists should
see as the opportunity of the organization, is that through its
website, its newsletter, the opportunity to really have a forum to
discuss where neuroscience impacts society. And it’s more than
just a discussion. I think the organization has grown to really see
its mission to develop strategies to meet the challenges head on.
Neuroscience is a rapidly growing field. There are many issues
that are now coming to bear that public discussion and
interdisciplinary open interactions is really going to be the way we
solve the problems. So I invite you to check out the website, and
the cost for students is really quite modest and the meeting is quite
fun, so thank you.

[Carlos Belmonte]: We will proceed with this
session. I will make a few comments and then our invited
speakers will present their ideas on the subject.

As brain researchers of a certain age, and
this includes myself, witness an astonishing development of
neuroscience along their professional lives. We are today in the
same city, in which Cajal, in 1888, advances the neuron theory, proposing that the nervous system was primarily composed by individual cells that were connected by contiguity, not continuity, thereby integrating modern neuroscience. Since then, in a bit more than a century, we collected a vast knowledge of the normal and disabled brain at the molecular, cellular and integrated levels. All together, it is not unrealistic to affirm that neuroscience advanced through a solid path in deciphering the biological mechanism that sustains sensations, movements, emotions and the most sophisticated cognitive processes, including consciousness, a goal that was considered out of the reach of the human mind only a few years ago.

In parallel with these advances, diseases of the brain are becoming one of the principle personal, social and economic burdens for countries in the developed world. They are pushing the scientific understanding of brain disorders at the frontier of modern biomedical research. The cost and burden of major brain disease in Europe amounts, according to the European Brain Council, €386 billion per year, and is increasing exponentially with the aging of the European population. Such tremendous
economic, personal and social load fully justifies the urgent need for a better scientific knowledge of the impact and disabled brain, and justifies the inclusion of brain research as one of the top priorities for modern science.

Certainly, there are other important health challenges as cardiovascular diseases or cancer, that also deserve urgent attention. But neuroscience research has additional distinct characteristics that plays the study of the brain far beyond the medical implications. Neurosciences are dealing with the scientific understanding of the organ that makes human beings unique, that sustains and determines the peculiarities of the individual and collective human behavior.

No other area in modern science offers such a powerful possibility to influence our personal and communal life as brain research does. Understanding the brain will expectedly modify many of our current social values. It will force us to consider the constraints and limits imposed by the biological characteristics of our brain, to the most cherished aspect of human nature, such as personal freedom and responsibility. Progress in neuroscience will expectedly change our views about justice,
violence, pleasure seeking, interpersonal relationships or children’s education, just to mention a few.

Accordingly, along the last decades, many leading neuroscientists became aware of the formidable ethical challenges that could derive from the progressive opening of the brain black box. Some philosophers, intellectuals and influential opinion leaders, from various fields, also realized that specific ethical implications derive from the advances in brain research. The conference, Neuroethics: Mapping the Field, sponsored in 2002 by the Dana Foundation, has been created as the formal origin of neuroethics as an independent discipline.

In the introduction of the aforementioned conference, neuroethics was delimited in the words of Bill Safire, as “A distinct portion of bioethics which is the consideration of good and bad consequences in medical practice and biological research.” He further wrote, “Considering that the power to examine and manipulate the brain offers the potential to change lives in profound personal ways and in an ever present reality, how will we make wise decisions about its use? How will we define and protect the integrity of our ability to judge morally and conduct
ourselves ethically?” Finally, neuroethics was defined by the Conference as the study of the ethical, legal and social questions that arise when scientific findings about the brain are carried into medical practice, legal interpretations and health and social policy.

Indeed, brain research is becoming increasingly relevant to a number of professional and academic disciplines beyond its traditional medical applications. Lawyers, educators, economists and business people, as well as a scholar of sociology, philosophy, applied ethics and policy, are incorporating the concepts and methods of neuroscience into their work and ethical evaluation of these activities became necessary. Besides, neuroscientists are confronting more and more every day the dilemma of conciliating possibilities of brain manipulation through genetic and molecular modifications, drugs and instruments, with the right of individuals to preserve their intimacy and to use their free will for themselves and their children.

Thus, neuroethics is a new and rapidly growing discipline that concerns neuroscientists in its broader sense, very directly. The attendance of this session is an example of such interest. We are going today to deal with a very specific
example of the ethical issues associated to deep brain stimulation, a new and promising technology that enables the treatment of a growing number of neurological and psychiatric disorders, but being an invasive procedure of the brain inevitably raises serious ethical interrogants, and these are many. We need to think whether an invasive surgical procedure is useful for effectively treating disorders where genetic susceptibility, developmental abnormalities and environmental stressors all play a part in these problems. It is right to offer vulnerable patients experimental forms of treatment. How do patients and referring physicians decide what protocol is best? How well is well enough to justify an invasive procedure? Is it right that the diversion of the deep brain stimulation method from dealing with brain disorders which themselves are difficult to define, to tinkering and enhancing the normal healthy brain?

These are a few of the ethical questions raised by a group of world leading experts in the therapeutic use of deep brain stimulation. They have been invited here today to discuss their experience and reflections on this procedure, that they are already using for treatment of motor as well as psychiatric
Our inviteds are: Helen Mayberg, MD. She’s a Professor of Psychiatry, Neurology and Radiology and the Dorothy Fuqua Chair in Psychiatry, Imaging and Therapeutics at Emory University School of Medicine. She’s a neurologist trained at Columbia’s Neurological Institute in New York, with fellowship training in nuclear medicine at Johns Hopkins. Helen heads an active research program studying brain mechanism mediating depression, pathogenesis, antidepressant treatment response using neuroimaging and pioneering the development of deep brain stimulation for treatment of resistant depression.

Our next speaker is going to be Damiaan Denys. He is Professor and Chair of the Department of Psychiatry at the AMC Amsterdam and Group Leader at the Netherlands Institute for Neuroscience. He was awarded the Ramaer Medal from the Netherlands Association for Psychiatry for Outstanding Clinical Research in Psychiatry. His scientific research is characterized by a translational approach. Damiaan conducts clinical and neurobiological research into anxiety and compulsivity and has played a leading role in the development of deep brain stimulation
for psychiatric disorders such as obsessive compulsive disorder, depression and addiction.

John Rothwell is Professor of Human Neurophysiology at the University College of London, and his research interests are focused on the physiology and pathophysiology of human movement and, hence, in Parkinson’s disease, Tourette syndrome and dystonia, some of the prime targets of DBS, deep brain stimulation. His recent work has focused on the long-term effects of DBS in patients with dystonia. He is now particularly interested in the field of noninvasive transcranial brain stimulation using techniques of transcranial magnetic brain stimulation and transcranial direct current stimulation.

Finally, Roger Barker is Professor of Clinical Neuroscience and Honorary Consultant in Neurology at the University of Cambridge and at Edinburgh Hospital. His main interests are in the degenerative disorders of the nervous system, in particular Parkinson’s and Huntington’s diseases, combining basic research, looking at cell therapies with clinical based research. He is the coordinator of Program Seven Transeuro Project looking at fetal cell grafting in patients with early
Parkinson’s disease.

We will start by listening to each one of those speakers, but after we will maintain a dialog among questions made by this table, followed by questions from the audience. I wish to emphasize that questions have to be short, precise and do not contain comments or opinions. Please try to be concise in the way you ask questions so that many people can participate. And I think we start with our first speaker, Helen.

[Helen Mayberg]: So I’m going to start this off by using the example of brain stimulation for treatment-resistant depression. I just want to quickly go over my disclosures. This is work, all of this kind of work does involve interaction between academia and device companies and I work with several, and some of the work has led to a patent that is now part of a large-scale clinical trial.

I think that depression is an example, but DBS for psychiatric disorders, more generally, has to start from an ethical framework of the scientific question itself, what is the target? What’s the rationale to be considering putting an electrode into a patient, particularly a patient with a disorder of behavior? What’s going to be the trial design? Who are you going to select to
actually do the testing on? And how does one make assessments of safety and efficacy? And many times this actually starts in an academic environment, and not directly by industry. But because we’re dealing with something where the hope is that anything that would be developed would actually be translatable to patients who may have need, the academic industry interaction has to be preserved. Generally, it goes in one direction and once things are handed off to industry, sort of the academic mission kind of goes on its way onto another topic, but I want to raise one particular scientific point to begin, is that maybe we always have to be considering that it should remain bidirectional because what one does to go to a clinical trial isn’t necessarily the final form, even if it becomes the final way in which a trial is done.

So some of the things to keep in mind is, what is the threshold to proceed to a trial? Do you need an animal model? And if so, what animal model should you use? I don’t actually know a rodent that actually can tell me about guilt and psychic pain, even though you can test in a rodent whether or not they’re anhedonic, and the question is, is whether or not that’s good enough, and whether or not there are models of treatment
resistant depression of which there are none in the rodent community.

What should be the nature of these trials? What kind of outcome measurements? What kind of response timelines? And how do we insure that scientific refinement can occur once trials proceed? Our approach was to basically take a clinical model based on imaging work, do a very routine, really leverage what had been done in Parkinson’s disease, to target an area of the brain that our work suggested was critical for antidepressant response.

We implanted classic, or standard, DBS electrodes in the subcallosal cingulate white matter, use standard and routine high frequency stimulation, and tested it in a group of treatment refractory, major depressed patients. We started with six patients, we got a good response in four of them with an open-label study. We extended it to 20 patients. We saw a sustained 60, 65 percent response rate out to a year. We followed those patients long term and saw if you got well, you stayed well. And from an academic point of view, we marched forward trying to get an idea of who the right patients were, what was the characteristics
of the patients we had studied. The public work was picked up by others because always seeing replication is critical and the group here in Barcelona were the second group to actually do a case series of studies on depressed patients in this target. This was expanded to St. Jude Medical, who did a pilot study to look at whether or not it should be extended to a full-scale clinical trial, and my group in Atlanta extended the work further to look at patients with bipolar type 2 disorder, and basically now about close to 70 patients, open-label studies there, looks as though there’s at least a signal to follow that patients with otherwise intractable depression can respond to this intervention. Other targets in the brain have been studied, notably the ventral capsule, ventral-striatal area, which we’ll hear about more in a minute; directly into the nucleus accumbens. There are targets that people have thought about and reported on case reports.

This has been picked up by the media as being the next new wave. So despite the fact that this is really still at an experimental stage, moving toward full-scale, randomized, double-blind, sham-controlled trials, the issue is, is that there’s considerable therapeutic misconception at this point, and the
question is, is that actually even the right term, that in order to know if something really is safe and effective, and when we’re dealing with implanting a device in someone’s brain that will be, that has the risk of surgery, that has the risk of infection, that has the risk of damaging the brain, that will be permanently implanted and that someone will wear and own a device for, as far as we know, forever; that what is the standard that we need in order to offer that?

How does a doctor with their patient even decide which of the available targets in the brain might be best given that you have choices? Should this be reserved for people who are intractably ill but stable, as it is now? How does one handle, actually, the very patients who have major depression in this situation, who are often suicidal, very unstable? They’re currently ineligible for a trial because it wouldn’t be safe to subject them to the demands of a trial, nor could a trial actually determine whether it was working.

Should the eligibility criteria be restricted? What about people with comorbid conditions? And if it’s safe and based on the plethora now of studies that are being done, why do
we wait for trial results to be completed? Again, that’s not my view, but this is the view that happens when small studies that show promising results move to the next step with CNN coverage, 60 Minutes coverage, The Economist coverage, The Guardian coverage all over Europe, all over the United States, as though we already know the answer.

Should patients have continued access to an experimental treatment if perhaps the trial fails but it works for them? Should they be able to have access, and if so, if it’s an experimental device, who’s going to pay for that? Who’s going to be responsible for that? Who’s going to take ownership of that? What happened if it breaks? What happens if the battery wears out? What happened if the company is bankrupt? These are things that you suddenly have to think about when you have a device that you didn’t think about at all when it’s a drug. A drug doesn’t work, they take your pills away, you go about your business. You have a device in your brain and suddenly a trial is over, do you get to keep it? And if not, who’s going to take it out? And is there anybody home to actually take care of that for you?

I think the other point is, when does an
experimental procedure become a treatment? And again, when things move quickly for public awareness, but we actually don’t know the true efficacy done in the most strategic and organized way, we move quickly for patients to feel as though, particularly desperate patients, that with intractable illness, suicidality, why should they be forced to wait? Because three years for a trial to be done and reviewed by the FDA or CE Mark or whoever it is, may be beyond what people can do. And that really brings the issue of beneficence and the justice argument. If you have people that are so ill that the thought of ever being well is actually out of their frame of reference, a patient’s perspective is, and I hear this all the time as patients call, hoping to be enrolled in our small research trials, if it’s safe, why should I have to wait for the randomized clinical trial results? And how good is good enough for me to have access? And if I have the money and I’m willing to take the risk and I have nothing to lose, why do I have to wait?

So the last point I want to make is, to switch gears slightly, is the issue of brain stimulation in a real world context because the issue is, what actually is that we’re doing for these patients? I think that a critical issue that you’ll hear with
everybody’s comments is the notion of framing expectation. When you are this ill, all you want, if you expect anything, and these are patients, by the time you’ve failed 12 drugs, 100 ECT rounds, every kind of psychotherapy known to man, the notion that anything is going to work, is actually beyond your frame of reference. But on the other hand, you’re willing to make an effort, if there is a trial to which you can enroll. And the issue is, is at that point what you want, or what patients explain, is they want the pain to go away, and that’s all they care about. The issue is, is that once the psychic pain or the primary symptoms are gone, then the issue is the real hard work starts, and the question is, what do we expect of these interventions? Do we expect them to help you get a new job? Make you feel motivated for the new job? Help you to know actually how to mobilize to consider the resources that you’ll need to bring online to get that new job? Or do we expect it to just remove the primary elements of the illness and return a patient to the ability to move in the direction of making their own way through therapy and other interventions? And I think that we develop a responsibility now as we take on patients of this level of disability, to know precisely what we’re doing with these interventions to be
able to have new ways to quantify what we can do and what we can’t do, and to frame for patients the part that the device can do, and what that enables them to be able to do themselves, and to then provide the resources and the access to ways to help them to be the best that they can possibly be.

[Carlos Belmonte]: Thank you very much. Our next speaker is Damiaan Denys.

[Damiaan Denys]: Thank you. I think neuroethics is a big issue, and particularly in the brain stimulation. We announced that I am more involved in DBS for seven or eight years now, and I think we have treated 75 patients, 40 with OCD, 25 with depression, some cases with treatment refractory heroin addiction and eating disorders, anorexia. So what I would like to do is give you an impression of the efficacy of DBS, so I’m going to show you two movie clips of a nurse, she’s actually a nurse analogy(?) and she had OCD, and you’re going to see the first movie clip where she’s in an off situation. She has been treated for one year. She suffers severe OCD. And she has been in an off situation for eight days because of research purposes. The movie clip shows you how she is, and then in the next movie clip, you put it on, and
within 15 minutes you can see how she reacts.

- (MOVIE PLAYS)

[Damiaan Denys]: Okay, now she’s turned on and you will see her, the next movie clip, approximately 15 minutes, ten, 15 minutes after the …

- (MOVIE PLAYS)

[Damiaan Denys]: Okay, just an impression of how this may work, and you can see there are three major things that are particularly here in this case, or in DBS, if you compare it with regular treatments in psychiatry. First of all, it goes very fast, treatment effects occur within minutes, hours, and this is, unusually, of course, in psychiatry we use months, mostly, to have some effect. Secondly, the effects are absolute. There is a huge decrease of symptoms, sometimes 80, 90 percent. And a third thing which is amazing, is that it has a global effect, not just limited to the symptoms. As you can see here in this case, she talks about self-confidence and other stuff.

I’m going to just give you some cases, three cases, out of our sample, with very specific ethical questions. And I would like to question the principles of bioethics. So the first
principle is that DBS, or any treatment should benefit the patient, and this is difficult in the case of DBS. The case is here, it’s a woman, she was 24 years old, she came in our OCD sample. There’s a third patient, six years ago. She suffered OCD, symmetry and perfectionistic obsession, so a very ego syntonic kind of obsessive compulsive disorder. Taking her clothes on (sic) would take her six or eight hours a day. We treated her with the brain simulation, but we failed. We tried for one year, and actually she was a non-responder. She had less than ten percent response on the Y-box, the scale that we used to scale the symptoms. So she was a non-responder. And two months ago I saw her again, of course we see them regularly, because she wanted to keep the device and keep on the stimulation despite the fact that she was officially a non-responder. And two months ago she said to me, “Well, I’m so lucky that I was the second or the third patient in your trial.” So when I asked her why, “Well, I know that you exclude now patients with symmetrical and perfectionistic ideas because they are non-responders.” I said, “Yes, we do.” “Well, I mean this is a pity because in my case, I know to you I am a non-responder, but for me it really saved my life. Thanks to DBS
I can live again.” This is just a single case to illustrate how different the experience of treatment and treatment efficacy can be between a patient and a doctor, and particularly in DBS there is a huge gap between assessing efficacy as a doctor and what the patient feels with DBS.

The second case is again a complicated case. It was an artist that we treated. He was a painter, suffers refractory depression for over 25 years. He was 46, I guess. Very severely ill, completely apathetic, had no interest, no pleasure in his life. We treated him, the brain simulation (Inaudible), and he responded very good. Within four or five months he had a decrease of symptoms over 60, 70 percent. So he was, again, interested in life, started painting again, and as well, he took his artistic life, literally, so he started to drink and was a bit more impulsive. He started to enjoy life, went out and so on and so on. So he changed a bit, his person changed, but he said, “That’s how I am. This is my real me. This is my natural self. That’s who I am, who I was when I was 18, before my depression.” But this guy was married and he had a family. And his partner didn’t really enjoy his impulsive acts and enjoyment and drinking and so on, and artistic
expressions. So she came to us and she asked us if he could lower the voltage to make him a little more depressed so that he could fit within the family context.

This is, again, a very complicated ethical issue. What are we aiming for? What is a natural self? Even if patients recognize themselves as natural selves, there are other problems that occur because they don’t fit into the environment, into the context.

Okay, the last case is a very interesting case, a rare case, a girl 26 years old; she was as student, a very bright student, suffered severe OCD. She washed her hands for six, eight hours a day, 300, 400 times a day; very, very ill. Came into the trial, we started with DBS and we had a hard time to find good settings. As we know with DBS, it’s not just the implantation, we needed a long time to optimize the variables. And in her case it took us eight months, nine months, ten, 12 months, over a year, and we couldn’t find good settings. And each time, each two weeks she came to our hospital with her parents and she hoped that she could get better, of course, with DBS, but it was quite hard. And finally, I think, eventually, after 14 months, she said,
“Well, this is a good setting. I am relieved now. I feel happy. This is a very good setting.” And her parents were happy as well, the father and the mother and the whole treatment team was happy, of course, after 14 months. So we were all happy, but we continued, of course, to observe her and strangely enough, she still had her symptoms. She continued to wash her hands for days, had her obsessions, but she was happy. So what we did is that we made her artificially happy, but she had all her symptoms.

This is an extreme case where we induced happiness in a patient and this was a very tough ethical problem for us, for the team. So what would you do in this case? A girl, 26 years old, and you induce happiness and she still had her obsessive compulsive symptoms, so we decided to stop the stimulation because the duty of a doctor is not to induce happiness. This raised a lot of controversy, of course, with the treatment team, with the family, and even in the Netherlands, I could say. But eventually we went on with trying to find good settings and luckily enough, after again another four or five months afterwards, we found good settings and we could diminish her obsessive compulsive symptoms without initiating artificial
happiness.

So these are very short, three ethical cases out of our sample, that raise important ethical issues and are, in my opinion, are very complicated, and the ethical principles of beneficence, normal efficiencies(?) and ultimately of patients, they fail to solve these complicated issues. Thank you.

[Carlos Belmonte] : Thank you very much Damiaan. John Rothwell now.

[John Rothwell]: I think we’ve heard in those two talks some examples of the problems, the ethical problems that are facing some deep brain stimulation patients with psychiatric disease. I’m going to switch no and I’m going to, instead of giving you more problems to think about, I’m going to talk, give you some new facts to take home to try and expand the way we’re looking at this problem. So I’m going to look at DBS and mention two lessons we can learn from the more extensive use of DBS we’ve had in Parkinson’s disease, in movement disorders. And then I’m going to talk about some new ways of stimulating the brain, which open up the problem of brain stimulation even further.

First the lessons from Parkinson’s disease,
and the first lesson is that numbers are important; that you’ve got to look at and have experience of DBS and its outcomes in large numbers of patients before you can get enough evidence to give patients an informed decision about what the best treatment is. So it’s only now, in fact, that we are in Parkinson’s disease beginning to get articles like this coming out, that are consensus articles telling us what the best patients are and how to choose them, who will respond best to DBS, and what the likely side effects of stimulation are in each location. So, we can have conclusions like this, that say patients with Parkinson’s disease, without significant cognitive psychiatric problems, who have tremor, intractable tremor, intractable motor fluctuations, et cetera, are good candidates. This bit, without significant cognitive or psychiatric disturbances is very important. It took a lot of patients studied to realize that if you take those patients and you give them DBS for Parkinson’s disease, they won’t do very well at all, in fact they’ll do worse. And we know in Parkinson’s disease we can say to patients before we implant them, “If we’re giving you DBS in the subthalamus there are the possibilities, and we know what the percentages are, that you might have increased depression,
apathy, impulsivity, worsened verbal fluency and executive
dysfunction; your movements might be a lot better, but you might
get all these other things as well.”

Now it takes hundreds of patients to
determine these facts that are relevant for patients when
considering treatment in Parkinson’s disease. The problem we’re
going to have is in these other conditions where there are so many
different possible locations to look at, to get this amount of
information for each of those locations is going to be very difficult
and will end up with patients undergoing treatments on the basis of
insufficient evidence.

The second thing about DBS movement
disorders is that we’re always told that DBS is a reversible
technique and in most cases it is. That’s why people implanted the
electrodes all over the brain, for all sorts of diseases, just to see
what might happen. In fact, it’s not always reversible and there are
cases, especially cases in dystonia, which I’m particularly
interested in, where it’s not reversible. Here is a case report of one
patient who had dystonia, and I’ll explain what dystonia is in a
minute, affecting the face. And we see here, it says here, “Early
response to therapy proved treatable and reversible,” like we’ve just heard in some of the other patients.

However, after the fifth post-operative year, the patient gained independence from the DBS and has since been more than one year without treatment or exacerbation of motor symptoms. So in this person the DBS was stopped but the treatment effect was continued, was not reversible.

I’m just going to show you some more examples. This is a sort of patient with dystonia that I’m talking about. This is a patient who’s got a severe, generalized, childhood onset dystonia. It’s a genetic condition, DYT1 dystonia. These patients respond remarkably well to treatment with DBS in the basal ganglia. This is the same man two years later, and he is remarkably better, 80 percent or more better on the scales we use to determine these things. Now, we’ve been looking at these patients, and patients like this, in a trial with collaborators in Montpellier in France, and we took ten of these patients, as bad as the boy I’ve just illustrated, and they’ve been stimulated continuously for five years with DBS. At the end of the five years, they all came into hospital and they were withdrawn from DBS,
they were turned off for two days, 48 hours. Five of those ten patients didn’t change their symptoms at all. They didn’t deteriorate over the 48 hours. They were still better. Five of them got worse, as we might anticipate, but 50 percent, five of them actually remained symptom free, virtually. And, in fact, three of them remained turned off for more than two weeks, and they were still symptom free. They were still better. So we didn’t leave them turned off because they were going off on holidays and to other places where if anything could suddenly happen they would have been in trouble, so they would turn back on, but there was no medical need to turn back on. To all intents and purposes, they perhaps had had a permanent effect. So DBS may not always be the benign thing that people say it is.

Let me turn now to other ways of stimulating the brain, and I’m mentioning these because it opens the box to doing this in many other conditions, and made it very widely available so that you don’t even need a surgeon to do the implantation in order to stimulate the brain. So there are now two or three several methods, but these are two main ones for stimulating the brain externally, transcranially, once called
transcranial magnetic stimulation, and that uses a magnetic field to induce an electric current in the brain. The magnetic field sort of carries the stimulus across the barrier of the skull and gets it into the brain, and you can stimulate the brain externally quite easily, and that can cause neurons to discharge in the brain.

And then there’s this other form of transcranial stimulation called transcranial direct current stimulation, TDCS, and it looks a bit like this, and they have two electrodes on the scalp and you pass a very small current, electric current between them for 20 minutes or so. And both of these things can have effects on the brain and I’ll just illustrate one or two things to you.

The DC stimulation I’m mentioning here, it’s particularly something to look out for. Basically, it’s like having a nine volt battery connected across your head. You too can go out and do this to yourself later on tonight if you wish. Both these things do have effects and are, in fact, being used as treatment options. Repetitive transcranial magnetic stimulation is a treatment option for refractory depression. It’s used in the United States and it’s FDA-approved in the United States for the treatment of
depression. So these things, external stimulation, does work. It works in this case if you give the treatment every day for about six weeks to patients with medically refractory depression. It doesn’t give you the enormous results that you see from DBS. It has a significant effect, which is not unlike that that you see from drugs.

The C stimulation, the nine volt battery option, also seems to have some effects. There aren’t very many large trials in that, but here’s a recent one of using it in subacute stroke patients. This is to improve the response to physical therapy after stroke. They give it, they give the brain stimulation for 20 minutes or so while its patients are having their therapy every day for two weeks or so, and in this particular trial what you see is that the patients who are given the brain stimulation, the DC brain stimulation, do better than the patients who are given shock over three months. The treatment was for two weeks and they were followed up for three months. So these things do, do things, and they do work.

Because they’re easy to do, of course, people are also thinking of using these, like brain stimulation, deep brain stimulation, not only to cure people with disease, but to enhance
function as well, so there are, with these transcranial methods, it’s very easy to try to do this, to yourself, to other people. There’s a group in Australia who claim to produce savant-like skills in normal people by giving them TMS to improve their function. This is supposed to be improved artistic drawing after DC stimulation, here’s improved proofreading. Other people give DC stimulation, the nine volt battery to yourself during sleep at the right time and you can increase the number of words we culled from a word list to make yourself better.

So I’ve told you these things about the external forms of brain stimulation because, as you can see, they do have potential for therapeutic effects. People are using it for that. But at the moment the effects are small. But the ease of administration means it’s not possible to control the application.

Thanks.

[Carlos Belmonte]: Thank you very much. Dr. Roger Barker.

[Roger Barker]: I’m going to take a slightly different tack here. I’m going to talk about neurological illnesses and I’m going to talk particularly about Parkinson’s disease, and I’m going
to talk about what has already been done with cells and genes in Parkinson’s disease, and take you through the story of what happens if you put a growth factor into the brain and what happens if you put cells into the brain and you’ll see some similarities in the stories as they unfold. And I will try and draw out the ethical problems that have arisen, and the problems that have arisen in these therapies, as we move forward.

So, for Parkinson’s disease there have essentially been two major strategies for repair. One is obviously to improve the dopaminergic system which lies at the heart of the pathology in this condition by giving growth factors to promote repair within that system. You either put the growth factor in directly into the brain, or you put a gene which expresses that growth factor into the brain, or you simply replace those cells that are lost in part, namely the dopamine cells. Now, in order to take that to the clinic, which is what happens, you have to do that in the context of no suitable animal models by which to judge your therapy in the lab. You can show in the lab that your cells or your gene therapy can have an effect and the cells can survive, but of course, nothing in the lab looks like the patient with Parkinson’s
So one of the dilemmas is, at what point do you collect enough experimental data to feel confident to go to the clinic. And why would you go to the clinic with Parkinson’s disease, which is the archetypal neurological disease considered with these particular therapies? Well, it’s common, one in 800 people get Parkinson’s disease, it’s incurable, it causes major disability despite the drugs which are there to treat it symptomatically, and it has a very well defined core pathological event which gives you a target by which you can apply your therapy. That’s not going to cure people, but it’s at least a target.

So what has been done with growth factors? Well, growth factors, the one factor which has become the most prominent one to trial in Parkinson’s disease has been glial cell line-derived neurotrophic factor, GDNF. Originally it was infused into the ventricles, had no effect at all because it didn’t get into the brain, but Steve Gill, a neurosurgeon in Bristol, in the United Kingdom, did a study where he injected GDNF through a catheter directly into the brain, where the dopamine innovation, which is lost in Parkinson’s disease, should be. What he found was that if you
actually infused growth factor into the brain of these five patients, they significantly improved. I’m not sure I’ve got a pointer here that works, but basically, their motor scores improve as a consequence of having this infused. The patients felt better. This was all open label. Everyone knew they were having treatment.

Those patients not only improved clinically, but on imaging, looking at dopamine in the brain using fluorodopa, there was increased signal at the site at which the growth factor was infused, and one of those patients subsequently died from an unrelated event, I think they had a heart attack, and at post mortem, that patient was found to have sprouting of the dopamine fibers around where the GDNF was infused in the brain. So in its open-label study everyone knew they were having the treatment, both patient and clinicians; the five patients improved clinically, on imaging, and the one who died improved pathologically.

Ten patients in Kentucky had a similar treatment, and on that background of 15 patients, a double-blind placebo-controlled trial was conducted, in which growth factor was infused versus saline, into 34 patients, the conclusion of which was that it didn’t work. The consequence of that was that GDNF was
not given to anymore patients, so even those patients that had it and had a benefit, had it withdrawn from them. Was that right for the company that made GDNF to take it away from the patients, who clearly had improved, in the UK and the Kentucky study? Was it right to draw a conclusion that if treatment didn’t work on the basis of 32 patients? But those are the numbers you have to worry about when you’re actually doing invasive neurosurgical techniques, putting catheters into the brain and putting in agents. At least in this case you could say it was reversible up to a point.

More recently, because GDNF was patented by Amgen, making a gene therapy for GDNF was not possible, so a company called Ceregene did the next best thing, which was to make something like GDNF, which was Neurturin, they put that into a viral vector, injected it into the brain of patients with Parkinson’s disease, saw no significant benefit at 12 months, but did see a significant signal at 18 months. And so this improvement in clinical outcome was not mirrored by imaging, but the overall message which comes out from growth factors if you talk to people is that growth factors are an ineffective treatment for Parkinson’s disease, because in a double-blind, placebo-controlled trial, it has been
found not to work in a gene therapy trial, the effects at best are equivocal.

Now it’s important also to remember at this point, that these are biological agents. These are not tablets. These are not things you’re expecting to work straightaway. They will take months and years to work because you’re trying to promote the growth of the dopamine fibers in the brain. The other important point is the best time to give this will be the time at which you have the most opening fibers to rescue, which is the point of diagnosis, which in Parkinson’s disease you have at least 12 drugs you could give the patient, at the point they come to your clinic, which is the very time when this therapy may be more effective. And Ceregene, the company that did this trial, have just conducted another study where they’ve completed recruiting and treating patients in earlier stage disease, with infusions in slightly site.

Now, cell transplantation follows a very similar story. So in this, the strategy is to replace the lost dopamine cells in Parkinson’s disease. This has been done primarily by harvesting the dopamine cells from aborted fetuses. So you dissect out the developing midbrain from fetuses which
have been aborted for various reasons, you take that fetal tissue and you inject that into the brain where dopamine has been lost in Parkinson’s disease. And in the early open-label studies which were done mainly in Europe and in North America, the outcomes were, on occasions, very striking. So in the bottom figure here, this patient here is a patient who had a unilateral transplant of fetal dopamine cells. Before they had the operation they spent two thirds of the day off. That means despite taking the optimal drug therapy it appeared as though the drugs weren’t working. Three years after they had their fetal transplant, they went from being off two thirds of the day to being on all day in the face of stopping all of their medication.

So, clinically, this patient had done something you do not see in Parkinson’s disease, and that clinical improvement was mirrored by an increase in dopamine signal at the sight of transplantation, whereas in the non-transplanted site, you can actually see that the signal has gone down. The disease process has continued but not affected the transplant significantly.

So these open-label studies which were done throughout Europe and North America then led to the idea that this
now had to be the subject again of a double-blind, placebo-controlled trial. And there were two of these done in NIH. These studies involved 40 patients and 34 patients. So if you talk to cardiologists, they think you mean 40,000 and 34,000, those are the studies you’re talking about, these are absolute numbers. So the power to detect something with these studies is marginal at best. Double-blind, placebo-controlled trials in this context means that all patients go to theater, all patients have a hole drilled in the skull. Those who have active treatment have a needle put in and the cells injected; those who do not, they pretend to put the needle into the brain, and the patient and the clinicians who subsequently assess the patient, do not know whether they’ve had the operation or not.

In the second study, those patients in the sham arm also took immunotherapy for six months, with all the risks that that brings. So this creates major questions as to whether you should be doing sham surgery in trials of this nature. The outcome of these two double-blind, placebo-controlled trials, was that in neither study was there a significant benefit from having a transplant at the outcome endpoint, which was one and two
years, but some of the patients developed some involuntary movements associated with the graphs, so they were, therefore, producing side effects.

As a consequence of that, transplants of Parkinson’s disease finished in 2003 with the publication of that second paper. You can then say, well, they clearly don’t work, transplants, because they’ve been the subject of proper trials and a few side effects, but then you have to explain away these two patients at the bottom here, these are two patients from the UK who are transplanted in Sweden. These patients are now 26 and 23 years into their condition. They’ve both had a transplant 16 and 13 years previously. They have a UPDRS of Parkinson’s disease motor score which is less than when they presented to their clinician 26 and 23 years ago. They are on no medication, and their signal of dopamine in their brain is normal. So these studies clearly show that it works in some cases, but not in others. What do you do? Well, in Europe we’ve taken this forward in a trial called Trans Euro, which is essentially to illustrate how we take this forward, in that you look at the critical facts, you address them in the lab, you address what you can in the clinic, and then you move
forward in an iterative process with the hope that this will lay the groundwork for how you would take forward new therapists to do with stem cells.

Now, many of you will be aware that at the end of the last year, Lawrence (Inaudible) published which showed that it was possible to make safe dopaminergic neurons from a human embryonic stem cell line, which means that that will almost certainly be the subject of some clinical trial in the next five years. The critical question is, do we know how to do that? And I think the answer is we don’t. So I think how far have we got from a clinical treatment with cells and genes? Well, we’re there. And most people will say we’re there, we’ve been there, and we’re now past it, and that is a treatment that is no longer useful in Parkinson’s disease so let’s just consign it to history.

I would say that actually what we’ve learned is that we have no idea how to do these type of studies, and the results are extremely variable. And they’re very variable, because we don’t know how to test and that to take from the lab to the clinic to know what would be useful. We understand that Parkinson’s disease is much more complicated than a single disorder. We
don’t know when we should be treating a patient. We don’t know what patient type we should be treating, and also there are issues about consent, which limits who you can actually ask. We have absolutely no idea how to deliver these agents in terms of the optimal time in the disease; when we’re allowed to do it because of the alternative therapies that are out there; what dose you use in a patient which you can’t test in the lab; and where do you put that treatment and for how long? And how on earth do we measure efficacy? In that last transplant patient you may have noticed that 16 and 13 years after they had their transplant, they were still improving, these patients. So the endpoint of these studies may not be one year, two years, they should be better measured at ten and 20, and who’s going to fund that? And the question of sham surgery.

So I think we should view these experimental therapeutics as an iterative process. We should learn as we go along, the ethical issues are major with them, and we should not make ourselves a hostage to single to single, premature, double-blind, placebo-controlled trials. And for someone who works in the field, I cannot emphasize enough that these trials have essentially
finished the field for many years, and trying to bring it back to look at it in a more measured way, has been an extremely difficult process. Thank you.

[Carlos Belmonte]: Thank you. Well, I wish to thank the speakers that were so disciplined with time. Before we proceed with the questions from the audience, I would like to give the four of them the opportunity of asking, or making comments based on listening to the other speakers so that I will follow the same order and ask Helen, whether you want to make any comment or question or address something else?

[Helen Mayberg]: I’ll make a comment and ask a question. I think the really fantastic thing about this group of people is that, as a neurologist who does a psychiatric disease, I always figured we were just as at a disadvantage compared to the neurologist, because they actually really knew what they were doing. And it just kind of shows you everyone has the same set of problems. You think you know the element of the disease that you’re targeting, and you realize when you get into these new rationales, what we think we know isn’t really quite matching up to what we see, and so there has to be a real scientific equipoise
about what you expect to have happen and be prepared for actually the downside of things.

My question is, because it kind of came up in both Damiaan and John’s talk, is about the nature of discontinuation. I think there is some notion that somehow we all talk about plasticity and somehow if you are doing something, as everyone does basic neuroscience knows high frequency induces plastic changes, is what is actually happening? It was interesting with the dystonia, that you could give it and turn it off and actually you fixed it, so instead of seeing it as bad, not that it wasn’t reversible, for you it was good it wasn’t reversible. On the other hand, I guess the question is, are there equally cases where you actually lose the effect after turning it off, and if you turn it back on, was there actually plasticity that works against you?

And that’s sort of the same for Damiaan. Damiaan’s patients were, obviously that first woman, when it was turned off, it was really quite frightening how dramatic her deterioration was. We don’t see that kind of dramatic deterioration in the area of 25 DBS, although we do see loss of the effect over about two weeks, and it’s just not a rebound below where they
started, but rather, they are better. There is no plasticity. You may be able to induce neurogenesis in animal models with DBS, but if neurogenesis is required to have you not be depressed anymore it doesn’t work, not at two years, not at five years, not at eight years, that patients continue to require the stimulation. So I’d like to know about the discontinuation.

Roger Barker: I’ll just say briefly, the discontinuation effect, persisting, I think it won’t happen in all diseases, it doesn’t happen in Parkinson’s for example. Dystonia and some of what you’ve done, are condition where when you give DBS you don’t get immediate effects. In dystonia can build up over months, in fact, to a plateau. It may be in this sort of condition that we are seeing some sort of brain plasticity. It is strange, at a conference like this, where a lot of people are talking about brain plasticity, you put something in the brain, it stimulates thousands and thousands of times a day, and the night, and apparently it doesn’t do anything to the plasticity of the brain. Well it doesn’t in some diseases, but I think in other diseases, it probably will. And you leave it in long enough, as we’ve seen in some of our patients, it seems to have a permanent effect.
[Damiaan Denys]: Yes it’s true that we, of course, are using another target, the acumel area and the internal capsule. And in all our patients when we stop stimulation there is a huge relapse, even a rebound effect, so people are worse, or particularly on the mood level and anxiety level, than they were previously at baseline before they had the DBS.

I don’t know how to understand the effect. It might be a brain thing, so neuroplasticity, but it might well be that in these patients, once they have had the feeling that it went well, that they improved, going back to a previous state is worse. So it might be their subjective impression as well, so I don’t know whether this is a mind thing or a brain thing or both maybe.

[Carlos Belmonte]: But now we are in a more relaxed way. So do you want to take any economical question.

[Damiaan Denys]: Well, two things, I mean what struck me, the whole panel is that for these new therapies, genes or stem cells or DBS, whatsoever, we struggle with the design. It’s like to get approval in all these countries we rely on very conservative viewpoints where we use pharmacy trials as a kind of template but they do not fit. I mean we need another design. We need to think
about the designs that fit the DBS and these new therapies, and that’s just one comment I would like to make.

The other one is regarding treatment refractoriness. We know that these therapies are very helpful. They’re very effective and treatment refractoriness is mandatory now as a criterion. Should we keep it or should we loosen these criteria?

[Roger Barker]: I think it’s very interesting is because for Parkinson’s disease, the patients who are likely to do best are the patients who are not refractory to any treatment, they’re the ones who’ve not been exposed to any treatment. So this creates a huge ethical dilemma. And it’s not that you’re going to cure people with Parkinson’s disease, but you can imagine, for example, if you take someone of the early Parkinson’s disease, you give him 100,000 dopamine cells, or some growth factor, you keep their dopamine system going very well for five, ten, 15 years, they don’t need to take any drugs. They will get no complications from the medication. You haven’t cured them because the disease will carry on, but you have dramatically changed the landscape of treated disease.
Now, what will the ethical committees say when you say I want to take patients at that stage and treat them? It’s a much harder call than when you say, well we’ve tried everything, or we have a disease, for example, like Huntington’s disease, or motor neuron disease where you can say, well here are no therapeutic options. So we’re looking at therapeutic nihilism here, so let’s have a go. And I think this just raises another question, which I just wanted to sort of throw back at the panel, which is one of the problems we face in the world of cell therapies at least, is of course this stem cell tourism, that there is a huge amount that out there on cell-based therapies, all of which gets bracketed in the same way as lots of the therapies we’ve talked about, for which there is no scientific rationale at all. So, discriminating between what is actually scientifically sound to try, and then secondly, what is ethically sensible, or allowed to do in patients who have diseases for which there are therapeutic options.

[Helen Mayberg]: I’ll make a comment. I think on the first issue of the, to be intractable is the only reason you’re allowed to participate. I think when you have degenerative disease, it
becomes obvious. In psychiatry, again, with all of the back history on operating on psychiatric patients, the conservatism to take only people who had failed everything, the danger was that you would be beyond anything working, and as it’s turned out, that isn’t true. On the other hand, the treatments that we’ve acquired, namely electroconvulsive therapy, can actually do harm, and by the time you actually decide to have ECT and then by the time you’ve had enough medications, many years have gone by and you’ve kind of removed people from their life, so while the intractableness may be one criteria, the time disability becomes another criteria, and even if you get people better, the train has left the station. People don’t have the opportunity to go back to the job that they used to have, that even if they’re well … my first patient in Toronto was a nurse in the very psychiatric hospital where, community where we did the procedure. They refused to actually give her any kind of job back after five years being out of it. So you see that the stigma towards psychiatric disease, that being able to move earlier in the course of these people’s illness, particularly if there is a chance to change the course of their illness from intractable, or to prevent intractability, is something we’re going to have to deal with and I
think if the data supports it, waiting until people, because of time, or because of number of treatments, to meet that level of severity is not in the patient’s best interest.

[John Rothwell]: Just one comment. I think what we’ve all four said is that we’re now faced with the dilemma, where we’ve got potential treatments that might work, but we don’t know how to design trials to show whether they’re worth applying to more people. So what are we going to do? We’ve got … what are you going to do in your trail when you have to wait 15 years to figure out whether the treatment has actually had a worthwhile effect? How can we design? And if we can’t design trials like this, should we give up?

[Helen Mayberg]: You know, it’s funny because … it’s not funny but it’s distressing because, in fact, again, one wants to have rigor for design, and there are regulatory bodies that make these decisions, but I think the idea of the iterative design, the Bayesian design, is going to have to, you know, that can acknowledge that. You do a small number, you actually earn something and you make an iterative change. And I think this is proven true in the psychiatric field, the idea that … I mean it’s
actually quite tragic, it happened with vagus nerve stimulation, that you design a trial based on a drug trial and that somehow six to eight weeks or 12 weeks is long enough without really enough information except open, non-placebo controlled trial, to make your decision. And like pharma now, if you aren’t successful with your first try, the company ... it’s too expensive, will abandon what may be, and again, what may be a viable intervention. So I think the danger is just not we need new models for trials, but in fact, if we’re not smart enough, fast enough, possibilities will actually be shelved and we’ll see the ventral capsule, ventral striatal target for depression, that Medtronic was running for depression, was so shelved. And it’s probably all because of design. And that would be, you know, before you know if it works or doesn’t, would be an absolute tragedy for patients who need options.

[Roger Barker]: I was just going to say two points, really. One is, I think we’re very impatient. And obviously if it’s commercial then there’s a reason for that. But if you look at the NIH first study which was negative, published in the New England Journal, if you look at the follow-up study at four years, they had a significant benefit from the transplant. So if you’re prepared to
wait, you will see the signal, whether it’s real or not, but we’re not prepared to wait, and that is a problem. Secondly, we are hostage to a primary endpoint, so we often just say we’re going to have one primary endpoint, because that’s what we’re told. And if you don’t hit you primary endpoint, you’ve had a failed trial. I mean it’s a gamble that you know what the primary endpoint is. We should be much cleverer about this and have multiple endpoints by which we can look at vectors of change to see whether we’ve actually had an effect. So I think we have to have longer trials and we have to get away from a single endpoint

[Helen Mayberg]: That is the beauty of having an implant, because unless someone turns it off or removes it, you actually have the naturalistic experiment, and that is actually proving to be true as well in psychiatry with the transplants.

[Damiaan Denys]: Another thing is that, particularly in psychiatry, I have the impression that their assessment scales fail, other things change and we are focused on a few symptoms based on a very, on a disorder based on subjective criteria, the DSM, and so on. Again, with these new therapies we see other changes that are much more fundamental, so we should rethink our assessment
scales because we miss, as well, treatment effects.

[Carlos Belmonte]: Shall we perhaps, I think we should now go to the audience and listen to the questions raised by the people. Please feel free to stand and make a short, precise, focused question. Eva?

[Female Audience Member 1]: I don’t know whether it’s short and precise, but I would like to say something and ask you some questions about stem cell therapy, because stem cell therapy is a different problem than, for example, deep brain stimulation. And in stem cell therapy, the people are using different products. The companies are producing the stem cells which can differ enormously, and they can be also applied by different way. So what is your opinion about it? I’m not really surprised that one clinical study is not having effect, another one has effect, because the procedure which these clinicians are using, you know, being addressed by the company which is producing some product which they want to sell and make money out of it, it’s very different from the others, other companies. So I wouldn’t really be depressed if the one study is not working and we should probably go on, so I would like to know your opinion about this
important issue. Because, you know, even the Parkinson’s disease, I think, this is an exact example how the cells were not … how the patients didn’t get the same cells probably. They were very different.

[Roger Barker]: So you make the very point that I was trying to make, which was that everyone equates stem cell therapy with Parkinson’s disease as being the same. The trials I talked about have a very sound, scientific basis. They are using not stem cells, they’re using feta dopamine cells from aborted fetuses, and there are ethical problems with that. But those have a very sound scientific basis. They are prepared and delivered in the same way, although each patient has their own unique transplant. Most stem cell therapies which are out there, which you have to pay for, have no scientific rationale for why they’re being used, and that is a cause for concern.

My own view is that if you are having to pay for any cell-based therapy, then that is not right, because none of these have been proven, they are experimental and they should be the subject of a trial. So I think one should put stem cell therapies, there are no stem cell therapies for Parkinson’s disease that have
any proven efficacy, or a scientific basis at the moment, and the
are different from the fetal cell based therapies that I was talking
about this evening.

[Carlos Belmonte]: Other questions? Please.

[Female Audience Member 2]: Thanks. I wanted to
know if all these treatments, stimulation or cell therapy, are there,
these people, is it possible, are you doing some genotyping or
sequencing of the genomes of these people to understand why it’s
working for some people, or why it’s not working? I mean is it the
practice or it’s not … or it’s too expensive?

[Carlos Belmonte]: Who wants to answer?

[Helen Mayberg]: So, if something’s in a clinical trial I
can say that the BROADEN study is not routinely checking that as
part of its kind of goal. On the other hand, experimentally, we’re
looking at epigentic changes over time, looking at baseline
patterns. The funny thing is, even though it’s small samples, you
have to have large enough samples to actually get a signal. So
what would it mean to see a genotype in 20 people, 40 people, 100
people? Probably not a lot. And the good news is, over time
people are getting better so even if they don’t make a six-month
endpoint, we’re seeing 75, 80 percent of people long term are actually doing well. So, again, it’s the right intention. The issue is, is what is treatment-resistant depression? And people haven’t been able to find genotypes for depression more globally. So to actually take these resistant people and hope we’re going to get a genetic imprint on a really small sample is a really great idea. That’s probably not going to happen, but people are trying to figure out who … I think the more salient question is, who are the right patients? What’s the right kind of endophenotype of the illness and genetics may be a part of it, but it’s not clear yet.

[Roger Barker]: I was just going to say, I mean it’s a very good point. I mean we try to do a meta-analysis of all the transplants in patients with Parkinson’s disease and had great difficulty getting hold of the data. But genotyping the patient to see who did well or not, or even in small samples might be helpful One question which has arisen is, given that Parkinson’s disease is heterogeneous, wouldn’t it be more sensible just to take a homogeneous group and take a genetic form of Parkinson’s disease, known form and treat that, and that is people have thought about, but there aren’t sufficient numbers at the moment to
merit that.

[Helen Mayberg]: The dystonia patients, is it variation, given the genetic ones versus …?

[Roger Barker]: The dystonia patients, the DYT1 dystonia patients, so it’s a genetic variety, tend to work very well. The sporadic dystonia is the ones that we don’t know much about the genetics because of the numbers often, generally don’t do quite so well. In that case, in fact, I suppose we are … thank you for reminding me, we are in fact looking at the genotype already, almost, as one determinant of who might respond well.

[Male Audience Member 1]: I have a question that has to do with money. Some of the issues that you raised in terms of selecting which patient reminded me a bit of death panels, you’re selecting who is going to get a treatment and who is not and we’re trying to come up with criteria. But you know that politically this is kind of a hot potato. It’s not … who is making the decision as to who lives and who doesn’t? But the question that I really have is, how much should we take into account the cost of these rather, maybe not working now but eventually will work treatments, but they may be available only to a very small number of people who
can afford it? Because, as we all know, our healthcare system is going bankrupt, so we’re creating a lot of treatments for the very rich.

[Damiaan Denys]: I think for DBS, it’s reimbursed and European countries, I think Germany, Belgium and other countries. The selection of the patient is based on a very strict protocol which is merely scientific rather than financial.

[Helen Mayberg]: I’ll take that on, because I think it’s an issue. If this actually works, then the question will be, everyone should have access. Are you American?

[Male Audience Member 1]: Yes.

[Helen Mayberg]: I just wanted context. We’ve tried to look at what the cost analysis would be, because in the States what these patients are doing is, what is the burden of a primary breadwinner of a family who hasn’t worked in five years? And since our social system, welfare is about to end, best I can tell, depending on how the election will go, that what does it take to actually support a family and what does it cost if actually one of the leaders in a family cannot work? The cost of actually having a course of ECT and being hospitalized for the level of extemise that
these patients require is actually exceeding what it costs to have the surgical procedure done, at the current level of cost that’s paid by insurance for Parkinson’s disease, and if there’s more demand, then the cost could theoretically come down; that when there are batteries that will be rechargeable that the cost of follow-up surgery for battery replacement will be eliminated. So I think that cost analysis is important to consider, but I think the cost of what it is to be intractably ill and not work, and actually have what are the best available treatments now are I think are extensive and I think they’re comparable. So I think that our job is to see if it does work, to figure out who is the right patient to actually not get into who lives and who dies and move from there. And if we actually have really suitable treatments where the efficacy is proven, I think we can work out those details because my patients are able to go back to work, and they’re not relapsing as long as they have the devices on them. So as these different things are tested, we’ll know, and those cost analyses will really be available.

[Roger Barker]: I’d just like to say that in the UK, in fact, for Parkinson’s disease, those calculations are done, or are being done. There’s a decision on whether to give patients DBS,
in certain categories of patients it’s already been calculated and, therefore, we know the answer. It’s a question of numbers, again, for the other conditions. You’ve got to have a large enough patient base and a larger, that experience, as to know what the range of response is, to be able calculate.

[Female Audience Member 3]: I think some of you are old enough to remember the GM-1 ganglioside story back in the early ’80s with Fidia, which eventually went belly up producing this and offering it, and it was used as a treatment. It was done in animals initially but then used as a treatment for stroke mostly, but then they tried to apply it for Parkinson’s disease to enhance sort of, I think the idea was that it would promote sprouting and that you would be able to have patients go for longer before their symptoms were intractable. And there was sort of a mass hysteria for a couple of years. I don’t know how else to explain it. It’s one of these things where lots of papers came out from different labs and different countries. They couldn’t crack FDA and get into the US, apparently, but they were doing lots of trials and publications and lots of people were convinced that it was wonderful for about two years, and then the whole thing came apart like a house of cards.
Do you remember that at all? Because I’m sort of wondering, this is sort of to Professor Barker’s point, I think, about when do you stop? When is it good and when do you stop? Nobody even talks about GM-1 ganglioside. But if you go back and look, there were all sorts of trials saying that it worked. And I just wonder, when do we say this double-blind study is good enough or that it’s not? That’s sort of an important point because patients care so much and the physicians care so much.

[Roger Barker]: You’re absolutely right. Let’s just take GDNF, I think, is a prime example. So you can say, well, there’s a lot of hype around GDNF and really it didn’t work. For me, the evidence is that it clearly does work, and the reason I say it clearly works is there are changes on scan that show there’s increased fluorodopa. There is post-mortem evidence to show that there’s fiber sprouting, and there’s a wealth of laboratory data to show that GDNF is trophic for dopamine cells. So there’s a very sound scientific basis to have it work. There is a clinical data which suggests that it works. The double-blind, placebo-controlled trial failed, and I would suggest that one of the reasons why it failed was that all of the parameters, or most of the parameters in that
trial, were very different from all of the open label studies that had been done previously. And, therefore, you’re comparing 17 patients in a double-blind, placebo-controlled trial, against 15 in an open-label study, and you’re assuming that somewhere in that you will clearly see a signal. I suppose the point I’m saying is that you need to critically appraise what’s going on there. The scientific rationale, the scientific basis and the data as presented as to what it’s telling you, and try and take away the hype and the spin and what people are telling you about what they think their agent is doing. And I think you have to move forward in small steps.

Now, the trouble is, if there’s a large commercial interest behind it, you don’t have that luxury. There is a huge steam train driving forward with it, and it’s, as we’ve heard, once you hit a certain point and get a negative result, like GDNF, Amgen just don’t want to invest in it, it’s not worth it, and they’ve bin it. So I agree, you have to be very circumspect about looking at the data, but that’s not to say all negative trials are negative because the agent doesn’t work.

[Male Audience Member 2]: Obviously, you do seem to be a bit skeptical about those double-blind trials. My question
would be pretty simple, what else do we have in terms of removing as much bias as we can in those trials?

[Roger Barker]: I'll just quickly address that. I think there are two biases you ever see in a trial. One is the patient-placebo effect, the other is the observer bias. So, interestingly, and certainly in Parkinson’s disease, experimental therapeutics, if the trial is funded commercially, there is a much bigger placebo effect, or investigator bias effect, one of those two, in the control arm. So they always do much better in the control arm. In the second NIH study, which had no commercial benefit to the investigator, the two-year endpoint in the patient who had sham surgery was that they got worse. So actually, placebo effects aren’t always seen in these trials. I think there is a bias. One way to get around it, which is what we’re doing in our trial, is that all patients are videoed, and then a third party assesses the patient independent of us.

[Male Audience Member 3]: I have a question about plasticity. You mentioned that there were some patients that started to do very well without stimulation after so many years. And I’m thinking about, for example, the patient that I’ve seen at
the third month of a colleague, who had these electrodes implanted, to study focus of epilepsy. And we were at a certain moment saying, like the patient has had a screen beside the bed, could see his own activity of his own brain directly. We were wondering like, could this patient learn to use biofeedback as a way to control his own problem? I’m wondering about this in a deeper sense. If you have now these fantastic, precise tools to stimulate, to measure also, these are maybe just steps on a further road, in the sense that you could use these, maybe you have a new brand of neuropsychiatrists, that could study precisely what’s going on during different treatments, and gradually, maybe come to much simpler tools in which the patient learns to have more awareness of themselves, and maybe then just using this little battery that stimulates, of EMDR, which we are talking about, or maybe combinations with psychiatric drugs like Prozac that is changing critical periods that might help with these kinds of treatments. So I’m wondering what’s your view on this?

[Carlos Belmonte]: Thank you. Who is going to …?

[Damiaan Denys]: I think it’s a principle of neurofeedback. It’s a good point and what we could do, of course, with the
electrodes is not just stimulate the brains, but as well record brain activity during a certain amount of time, of course, post or surgery, we, at our hospital we have three or four days where you can record with the electrodes. We could try and train the patients to modify their own brain activity. That’s a very nice suggestion.

[Helen Mayberg]: One of the things that many people are trying to do is actually, and it’s always asked, can you actually down regulate area 25 yourself? And the issue is, is people do real time FMRI and actually, when you’re this sick, the biology shows you don’t have access to it, and by stimulating you actually bring it back online. So the issue is, is we see, not by, and again, can start to actually get a real-time read out, which new devices are being able to do, is actually, no, you may not need it on 24/7. You may actually learn how to tune it yourself with neurofeedback. But what we do know even now, is that with it on, if you put patients into cognitive behavioral therapy, they will describe how when they try to do therapy before DBS, they could go through the cognitive motions, but actually couldn’t kind of synchronize cognition with their feeling state. And with the stimulator on, they actually can learn it and use it. The issue is though, that those
same patients, when the battery is depleted, seem to go back to
the previous state and seem to lose access. So the question is, is
there something fundamental about people who reach these
malignant levels, at least in the psychiatric domain, that actually
the stimulation doesn’t actually normalize it, but allows it to work
more functionally. And I think when these devices evolve, because
of questions like yours, and that we have ways to actually look at it,
we’ll be able to know because we’ll be able to test it.

[Roger Barker]: I’ll just make a small comment, I think
it’s really a very interesting idea that you have there. After all,
there are groups around the world who are using biofeedback from
EEG electrodes for epilepsy and claiming a reduction in seizures
just by looking at the EEG. So it could be a very interesting idea to
try and incorporate the sort of biofeedback into the stimulators,
especially the new stimulators which that are becoming available
that are easily reprogrammable and could be controlled like that.

[Carlos Belmonte]: I would like to end with the bad
reputation of Spaniards are non-punctual people. We have started
seven minutes, ten minutes after the normal hour, but we will
finish, more or less, exactly after the time that we were allotted.
I wish to thank first the two institutions that promoted this meeting. It is obvious that there is full of new questions. I think we should look also to the history of medicine that is full of attempts, some of them dramatically an successful and others extremely successful, made with a very poor scientific background, and that also is something we need to take in consideration because in many cases we can not advance with the security provided by the scientific knowledge in some therapies. Obviously this opens up a cake that hopefully next Society for Neurosciences Meeting, FENS meetings, neuroethics will come more and more as part our daily activities.

And I would like to thank first the speakers for their clear and precise presentations, the audience for their very intelligent questions, and to organizers for doing this possible. Thank you very much.

(APPLAUSE)

(END OF TAPE)