インタビュー

うつ病に対するDBSの効果と今後の展望*
―Andres Lozano教授インタビュー―

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Effectiveness of DBS for depression and future perspective
―Interview with Prof. Andres Lozano―

(Interviewed by Chieko Kurihara [1], Takeo Saio [2])

1. Future study plan

――First of all, I heard in your lecture that you are planning to conduct a double-blind, controlled trial on DBS for depression. It is a very important process for this kind of experimental therapy. I would like to ask you the details of your plan. For example, how many sites and the kinds of areas that will take part in this trial?

Lozano The studies that are being planned, in order to get sufficient power, we must operate probably from between 100 and 200 patients. This means that we will need multiple sites because each site, in one or two years, can operate perhaps 10 or 15 patients. So this will likely require between 10 and 15 sites in North America to be able to generate this number of patients.

――You said North America. Does it mean Canada and the United States?

Lozano Canada and the United States, yes.

――How about including China? Aren't they interested in those as well?

Lozano They are but this will have to be sponsored by a grant or company, and so there has to be funding. It is very expensive to do this. And so we would only include people that are eligible for grant.

――So that is not a general academic study but that is sponsored by a company such like Medtronic?

Lozano It could be sponsored by either a grant, for example, government or by a company.

――It is aimed at getting some new usage of the device?

Lozano Yes. For usage of the device the company will be interested in that. But for scientific

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* This is the record of interview with Prof. Andres Lozano, when he visited Hamamatsu, to attend the Japan Society for Stereotactic and Functional Neurosurgery, the 25, 26th January, 2008. Interview was on 26th January.

Prof. Andres M. Lozano

purposes, the government will be interested.

——Concerning the design. Is this double-blind or one group is placebo or cross-over design?

Lozano　There are many potential designs. The one I think we will use is a cross-over design where everyone receives the implant and then the patients are randomized either to receive active stimulation or no stimulation.

——How long is the treatment?

Lozano　Probably between 3 and 6 months.

——How long does the whole study take?

Lozano　Six months.

——Is it possible for the subject to find out whether the stimulation is off or on?

Lozano　We don't think so because the subject will not feel when it is on. They cannot tell. So we think the blind will be preserved.

2. Perspective on global study

——This is a non realistic situation but I feel in some cases, I am working in the area of drug development, and sometimes in Japan it is very difficult to conduct early phase clinical trial and people are thinking about how they can join the Phase 3 study, skipping Phase 1 or Phase 2. In the early drug trials ethnic difference is very important. How do you think about the case of device development, is it possible to skip the early phases?

Lozano　Yes, I think. You are asking about the generalizability of the results?

——Yes. And I am thinking whether Japanese group can join in Phase 3 international trial without conduct Phase 1, 2, previously.

Lozano　So we will have a very specific inclusion criteria, exclusion criteria and our results will only be applicable to that patient population that we are studying. So if the decision is different in another part of the world, then that is a different problem and probably they should do their own study.

——In case of drug metabolism, dose-finding is very important. But in case of device, isn't it such kind of problem?

Lozano　The device is the same but the disease could be different. Just like metabolism is different, the drug is the same. So I think that any study that is done in the US may have to be repeated in other countries like in Japan.

——How about finding the target? Is it the same way in the US and in Japan?

Lozano　Yes because the brain is very similar; so I think that will not be a problem. It will be the same. It's like Parkinson's Disease. It is the same surgery in Japan and in the U.S. So this is like a Parkinson's Disease surgery except we are not treating motor problems. We are treating mood problems.

3. Effectiveness of DBS for psychiatric diseases

——I read your articles, these two [*1, 2]. I regard that these are the latest articles in which you de-

scribed clinical evaluation on human in the are of DBS for psychiatric diseases. Is this right?

Lozano Yes.

——You have disclosed 6 patients in this depression trial, and in the yesterday's lecture you said that you have about 28 patients?

Lozano 28 now.

——28 patients with depression?

Lozano Yes.

——And you added after these 6 patients?

Lozano Yes.

——Are you planning to publish some paper about these 28 patients.

Lozano Yes.

——Is there any difference between these 6 patients and the other patients?

Lozano No. They're very similar types of patients.

——So in these two papers concerning depression (*Neuron*. 2005 ; 45(5) : 651-60) and obsessive-compulsive disorder: OCD (*Neurosurgery*. 2007 ; 61(1) : 1-11), I think your perspective is different between these two disease areas. In OCD, you have not conducted this experiment, just reviewed literatures of other research groups?

Lozano Not in DBS for OCD. No.

——How do you feel, is there difference between these two diseases?

Lozano Night and day. Two different diseases; nothing to do with one another.

——Yes but you said that for OCD, it is not so efficient. I mean that I want to ask you how you evaluate the difference of efficacy between these two diseases.

Lozano No. I have not done work in OCD.

——You don't have any opinion?

Lozano I think that it needs to be studied but we don't know what the results are. I have enough to deal with depression; big problem.

4. Target area

——OK. Then, go back to depression. You describe something about the background story of how you identified Area 25. Could you describe briefly for our readers how you identified the process?

Lozano Dr. Mayberg is a neurologist who is interested in the anatomy of depression and she did two experiments. The first one was to ask which part of the brain is involved in sadness. And she did experiments where people are made sad; normal people were made sad, and looked for which areas of the brain became active or change during sadness. And this is how Area 25 was identified. It was the area of the brain that became very active during sadness. So based on this, it was suggested that Area 25 is involved in mediating sadness, and the more active Area 25 is, perhaps the more sad you are. So that was one piece of data. The second piece of data is that when patients are depressed and you give them medicine and they improved, and you look at what changes happen in the brain when they improved, the largest change is, the activity of Area 25 goes down. So from these two observations, we felt that Area 25 is important in causing depression and that one should look at if it is possible to turn down that Area 25 and to see whether that helps depression. This was the hypothesis of the experiment.

——Dr. Saio is a psychiatrist, but he thinks that sadness and depression are different. But he un-

*1 Lipsman N, Neimat JS, Lozano AM. Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: the search for a valid target. *Neurosurgery*. 2007 ; 61(1) : 1-11.

*2 Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2005 ; 45(5) : 651-60.

derstood very well from listening to your lecture that this stimulation of the areas of sadness may change circulation of the whole system.

Lozano　Right. This area may be involved in sadness but it is connected to other areas of the brain which control sleep, which control motivation, which control circadian rhythm, appetite; all these things are affected in depression. So it is possible that by intervening here in this one area, we can have an effect further away in the brain, in other areas of the brain. So you don't have to operate in every place; just one place and you get an effect throughout the brain.

――At this moment, is there any other study group which conducts surgery in the same area?

Lozano　Not on the same area; but other potential areas because this is the circuit in the brain and so it is possible to go elsewhere as well.

――Don't you have any idea to stimulate happiness in the brain?

Lozano　We don't know where the happiness areas are. This is not a happiness area because we do not make them happy. We stimulate; we do not make them happy. This is only sadness. So we do not feel we make the patients happy. We feel we removed sadness.

――Some specialists say that suppressed sadness causes the patient to feel apathy?

Lozano　Yes. We are not just suppressing normal sadness; we are suppressing pathological sadness. So we take them from pathological sadness to normal and then they are able to have sadness or happiness when it is appropriate. The trouble with these patients is that they are stuck in sadness. They are not able to get out of sadness. Always sad. Never out of sadness. So we bring them up to the surface and there they are able to be sad when it is appropriate or to be happy when it is appropriate. So we would like them to become normal and have a normal range of emotions. And it looks like they can have a normal range of emotions after the surgery.

5. Psychopathological analysis

――Another idea of Dr. Saio is that, in some

Interviewed by Chieko Kurihara, at the Congress Center, Act City Hamamatsu, January 26, 2008.
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studies, psychopathologists take part to describe the expression of subjects. In your experiment, there is no psychopathologist?

Lozano We have psychologists, neuropsychologists, to study psychiatric symptoms and functions and so on.

——In some kind of psychological study, there are psychopathologists who describe the internal experience of patients from the psychopathologist point of view. We think, from the view point of Anglo-Saxon psychological scientists, in the US and Canada and England, they seem to regard such study is not so important. So, there is no such kind of study?

Lozano There is. But we think that depression is a disease of the brain, of the circuits of the brain that are not functioning and our objective is to identify the circuits and to try to make them behave more normal. So we are not examining the psychopathological aspects of the illness. These are people who are very ill; who are not leaving the house. Some of them go back to work afterwards. So we are more interested in the science and biology of the illness.

6. Pharmacological treatment and ECT

——We can understand it from your explanation. So how do you think about the difference between pharmacological hypothesis and your hypothesis to stimulate depression patients?

Lozano We only treat patients that fail pharmacology. So if they are doing well with pharmacology they should not be operated on. So we only deal with patients that have failed the best available drug and have failed ECT (electro convulsive therapy). So we only take the most difficult patients who have run out of choices. They have no other option.

——The patients also fail to get cured by ECT?

Lozano Yes. That is why we operate on them. This is one of the criteria – at least 4 different kinds of drugs of sufficient time and therapy and ECT; and if you are still sick, then we will consider your surgery.

7. Discussion on ethics

——I would like to ask some ethical point of view questions. You said there are 3 ethics committees that review your study. One is the hospital, second is the university, and what is the third review?

Lozano We also had to get ethical approval for the PET scan.

——That is for assessment of radioactive effects?

Lozano Yes.

——Is there any discussion from the social point of view like yesterday's discussion? As you found yesterday, Japanese discussion on ethics is very premature level, hard to resolve ethical dilemma, in this country. I think you feel it also. But how do you think is that kind of discussion in neuroethics or some concern for the future situation, thinking of only one suicide case. I think you explained very well about this in the case of one patient, about their consciousness in taking part in the study. But how is the discussion among your society, scientific society, ethical society, at the national level. Maybe there is some discussion on this.

Lozano Yes, I think the discussions there are just beginning because this is new, and so they are now thinking about what are the implications, the ethical implications. But I think that it is very important to remember that these patients are very ill and that after the surgery they are better. So whatever the ethical discussion has to also take into account that it is unethical not to treat pa-

tients and not to help patients. So I think we have to protect and respect the patients but we must also not abandon these patients.

――You heard the point of view of the psychiatric society in Japan. This is a very miserable situation in Japan that they cannot overcome the memory of the history of lobotomy. How do you think about this? Did you experience this kind of discussion?

Lozano　Not so much, because we have argued that this is very similar to Parkinson's Disease. We are doing the same kind of operation. We are using the same equipment. We have helped many patients of Parkinson's Disease. So we feel that the surgery is relatively safe. We feel there are no permanent problems with the surgery because the surgery is reversible. If the surgery does not work, we turn the machine off or you remove the machine and the patient should be the same. He should never be worse.

――This is an opinion written in Japanese by the Psychiatric Society saying that they found negative results after reviewing these kind of literatures. The most important point is that some person said yesterday that a patient committed suicide after receiving DBS therapy. This is the OCD patient.

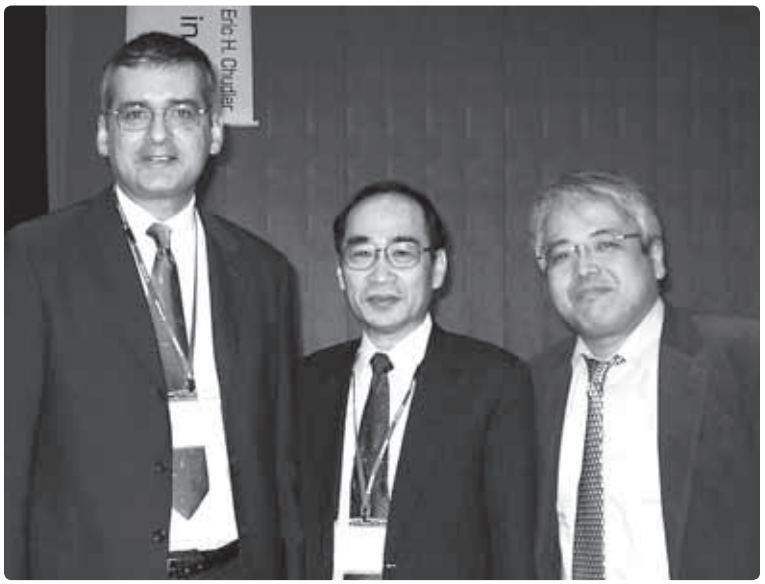
Lozano　Yes, OCD.

――You summarized this research result in your review article (*Neurosurgery*. 2007；61(1)：1-11).

Lozano　Yes.

――You did not write anything about this suicide case. I suppose, from your talk at the panel discussion, that you don't regard there is any relationship between DBS and suicide. At least, there is no evidence that the stimulation caused suicide.

Lozano　Well, these patients have a very high suicide rate. So whether you have operations or not they will still commit suicide.



Prof. Andres M. Lozano, Prof. Yoichi Katayama, Dr. Takeo Saio. Congress Center, Act City Hamamatsu, January 26, 2008. After Prof. Lozano's second lecture at the meeting.
左から，Lozano教授，片山容一教授，齊尾武郎.
2008年1月26日アクトシティ浜松コングレスセンターにて，Lozano教授の2回め講演終了後.

——Yes, I agree with you.

Lozano So the issue is do they commit more or less suicide than before. But you know this is just like having cancer. If you have cancer, you will die of cancer. So if you have depression, you will have a 15% chance of dying of depression from suicide. So it is very unusual that we have no suicides. So I think that tells you that this is probably pretty safe. But we expect that like any other disease there will be suicides in this. Whether the patients are operated on or whether they are not operated on, they will commit suicide.

——So it is necessary to compare the patients.

Lozano The issue is, does it increase it or decrease it or have no effect. So we do not know. Right now it seems quite safe. Maybe there will be no more suicides in the future.

——It is a very important point and your double-blind trial would be very important.

Lozano I hope so.

8. Future perspective

——Is there any cost-benefit analysis?

Lozano Not yet. We are still at the Phase 1 and Phase 2 stage. So it is premature to do a cost-benefit analysis until we have Phase 3 study.

——As far as this Phase 3 study is concerned, when do you think it will start?

Lozano We have to get approval from the government and we have to get funding. So probably within one year.

——So maybe next year?

Lozano Yes, hopefully.

——I hope that it will be approved.

Lozano I hope so. I think it will be approved because the preliminary data is favorable. So I think it will be approved and we will see what the results are.

——Thank you very much. That was a very good interview.

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