“The Illusion of the Perfect Brain Enhancer” with Alvaro Pascual-Leone

Transcript of Cerebrum Podcast

Guest: Alvaro Pascual-Leone, M.D., Ph.D., is professor of neurology and an associate dean for clinical and translational research at Harvard Medical School. He is chief for the Division of Cognitive Neurology and the director of the Berenson-Allen Center for Noninvasive Brain Stimulation at Beth Israel Deaconess Medical Center. Pascual-Leone is a practicing cognitive neurologist and researches the mechanisms that control brain plasticity across the life span. He is considered a world leader in the field of noninvasive brain stimulation, where his contributions span from technology development through basic neurobiologic insights from animal studies and modeling approaches, to human proof-of-principle and multicenter clinical trials. Pascual-Leone obtained an M.D. and a Ph.D. in neurophysiology in 1984 and 1985 respectively, both from the Faculty of Medicine of Freiburg University in Germany. He also trained at the University of Minnesota, the US National Institutes of Health, and the Cajal Institute of the Spanish Research Council.

Host: Bill Glovin serves as editor of *Cerebrum* and the *Cerebrum Anthology: Emerging Issues in Brain Science*. He is also executive editor of the Dana Press and *Brain in the News*. Prior to joining the Dana Foundation, Mr. Glovin was senior editor of *Rutgers Magazine* and editor of *Rutgers Focus*. He has served as managing editor of *New Jersey Success*, editor of *New Jersey Business* magazine, and as a staff writer at *The Record* newspaper in Hackensack, NJ. Mr. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: Many questions loom over transcranial direct current stimulation, otherwise known as tDCS. That in itself is a mouthful. What is TDCS? For those who aren't in the field, it's a form of neurostimulation in which low current is delivered directly to the areas of the brain using small electrodes. Brain stim was first used in the 1950s and '60s, but has seen rapid growth in the last five years. Originally, tDCS was developed to help stroke patients, but is now used to enhance just about everything having to do with the brain.

Hi, I'm Bill Glovin, editor of *Cerebrum* and host of the *Cerebrum* podcast. With us today on the phone is Alvaro Pascual-Leone, co-author of our most recent Cerebrum article, "The Illusion of the Perfect Brain Enhancer." We were very fortunate that Dr. Pascual-Leone was able to carve out the time to co-write the article. He's a world leader in the field of non-invasive brain stimulation. Both an MD and PhD, he's a professor of neurology and an associate dean for clinical

and translational research at Harvard Medical School. He is chief for the Division of Cognitive Neurology and the director of the Berenson-Allen Center for Noninvasive Brain Stimulation in Beth Israel Deaconess Medical Center in Boston.

Welcome to the podcast, Dr. Pascual-Leone. First, thank you for the wonderful article. People can read it at Dana.org. Let's start with, as I said in my introduction, brain stim was first used in the '50s and '60s, and is now rapidly growing. Why is that?

Dr. Pascual-Leone: That's a great question. First of all, it is a pleasure to be here. Thank you. I think it is a timely topic to address. I think that the reason why there's been a real resurgence of this technique is, in part, because the technology has improved, and things that were really not fully possible, although attempted in the '50s and '60s, seem realistically possible. It appears, thanks to the improvement in electrodes and the greater understanding of the kinds of currents and amount of currents that are needed to modify brain activity, it appears really possible to modify the level of activity in specific parts of the human brain through what is a very unintrusive and relatively simple technique.

Because it is relatively simple, it is also possible for people to at least try to make their own devices. And in doing so, there's been a real expansion and growth of a do-it-yourself community as well as the direct consumer devices industry that has been also catalyzed in the adoption of these methods.

Bill Glovin: Can you explain the difference between deep brain stimulation and transcranial direct current stimulation?

Dr. Pascual-Leone: Yes. It is an important difference. So, in deep brain stimulation an electrode, a wire is the word, is placed through the skin and the skull into the brain of the patient to specific structures in the brain. This is approved, for example, for the treatment of Parkinson's disease, where it is implanted into what we call basal ganglia deep in the brain structure; that's the part of the circuit that controls movements. The electrode is then connected through another wire that goes under the skin to essentially a pace maker, a stimulus generator, under the clavicle, under the collar bone of the patient, and provides continuous stimulation for years.

In the case of transcranial direct current stimulation, electricity's also used to modify activity in the brain. But different from deep brain stimulation, no surgery is needed. Instead, a very, very small amount of current in the order of millions of pairs, one or two thousands of pairs, is passed between two electrodes that are essentially two sponges that are placed on top of the subject's skull, on top of the hair or forehead. One is connected to a positive and the other to a negative pole, and the current flows between the two, and most of the current flows through the skin and not into the brain, but a small amount does go into the brain through specific patterns that depend on where exactly

you put the electrodes. That amount of electricity is not enough to make the brain cells fire, which is what actually deep brain stimulation ends up doing. But it is enough amount of current to modify how likely the brain cells are to fire when they are called upon it by whatever the person is doing.

Bill Glovin: In all the materials I've read about your work and career, the word "non-invasive" keeps popping up. It's even in the title of the kind of center you direct. So that seems to be a real distinction between the technologies. And is that, now, more popular, or is that just a whole different kind of segment of the brain stimulation area?

Dr. Pascual-Leone: Yes. So I think as we've seen a rapid growth of different forms of brain stimulation and different forms of ways to modulate the level of activity of the brain, what we call neuro-modulation technique, there's a big separation between those where surgery is required to make it possible, like deep brain stimulation, that often are referred to as invasive methods, and those methods where no surgery is required, and instead the brain activity is modified through the skin and the skull, and therefore we call it non-invasive. And they can be applied more easily to people with no specific illness that would require surgery.

It is not the case that they are non-invasive in the sense that one is not modifying brain activity. We are modifying brain activity, and that means that they need to be done with appropriate care and with appropriate attention and precautions, but it is non-invasive in the sense that it doesn't require surgery.

Bill Glovin: What disorders does tDCS treat most effectively?

Dr. Pascual-Leone: That's a very good question, and I think it's still a question to be examined. We really don't have good studies yet, in terms of large enough studies, to fully establish the indication, but there are a number of studies of fairly good sample size showing a benefit in patients with depression, particularly with medication-resistant depression. And that means using tDCS to target specific parts of the frontal lobe. There are good results in applications for pain for specifically what we call neuropathic pain, also for fibromyalgia. In that case, the electrodes are placed in such a form that they target the sensory-motor part of the brain, counter-lateral to the side of the body that is painful. There is a tradition of efficacy in epilepsy, in certain forms of epilepsy. There is a benefit in speeding up recovery from stroke, particularly when combined with the assisted physical assisted therapy.

So there's a growing number of indications. And I think perhaps a very important point to make is that one should not think of tDCS, or any form of non-invasive or invasive brain stimulation, as a single therapy. Instead, one should think of it as a tool that, depending on the parameters, including particularly the position of the electrodes and what parts of the brain are targeted, that have very different effects. Somewhat similar to thinking of taking medication. You can take medication for a bunch of different disorders, it just

depends on exactly what medications you're taking. In the case of tDCS, it is particularly the amount of current and where you put the electrodes that defines the potential efficacy.

Bill Glovin: Apparently, tDCS effects something called cortical excitability. Can you explain what that means in terms of brain function?

Dr. Pascual-Leone: Yes. So in the brain, we differentiate the brain cortex, the gray matter of the brain, and then the white matter, and finally the deep brain structures, the basal ganglia. It turns out that the amount of current that we apply and the flow of the current largely means that the impact of the tDCS is limited to the most superficial part of the brain, the gray matter. So it is modifying activity of neurons in that gray matter, in the surface of the brain. However, because brain areas and brain cells are so tightly connected with each other through specific connections in the form of networks, when you modify activity in one cortical region, that impacts the activity in remote brain areas because of the connection. So you can think of the targeted cortical region as a way to influence a network of connections.

In fact, we know that the influence on the network is interdependent on the state of the network. So it matters not only where and how you stimulate, but in what setting you're doing it, what the person was doing before or is doing during or may do immediately after the stimulation, will influence the effects of the stimulation.

Bill Glovin: You write that your colleagues are working to identify something called “brain fingerprints.” Can you explain what that is?

Dr. Pascual-Leone: As we've come to learn more about the brain, we're learning that one of the characteristics of human brain function is, as I was mentioning previously, that the brain works in networks. It is areas of the brain working together at a specific timing and order that defines each thing that we're able to do. We are able to talk, listen to this podcast, think about this topic, imagine situations, make decisions, all these abilities are linked to specific networks of the brain.

The structure and the dynamics of those networks vary from person to person. So if one explores the characteristics of those dynamic changes that take place in the brain overtime in any one of us, it turns out there are differences, but it turns out that those differences are unique enough that one can almost identify who the person is on the basis of the characteristics of that brain activity. Ultimately, that would lead to a phenomenon akin to a fingerprint that is an identifier of a person, but on the basis of the characteristics of the brain dynamics of the individual.

Bill Glovin: That's quite fascinating.

Dr. Pascual-Leone: The reason why those things are particularly interesting in the context of brain stimulation is twofold. One is similar to an Alexander Calder mobile sculpture. You need to perturb the sculpture, and you need to perturb the brain in a controlled way to fully capture its dynamics. And brain stimulation—non-invasive brain stimulation—becomes a way to introducing such a controlled perturbation. So to learn not only how the dynamics are when left alone, but particularly how the brain is responding dynamically when perturbed in a controlled manner, just like you would capture the beauty of the Alexander Calder mobile sculpture by tapping it lightly or by letting the wind interact with it. So that's one reason why it's important to think about this fingerprint, as it were, of the brain in the context of brain stimulation.

But the other one is because the brain stimulation, particularly when applied repeatedly, can modify those dynamics, can modulate the brain, and in doing so can potentially modify, literally, who we are. Of course, the appeal is that it could make us better, it could enhance our abilities. The appeal is that you can't know about problems of pathology, but the risk is that it could not do something positive, but ultimately have a cost in modifying those activities.

Bill Glovin: I was reading about an MIT study published in *Cell* about temporal interference and its potential to help Parkinson's patients who have been treated with deep brain stim, and that surgical technique comes with risks, like infections, stroke, bleeding. Can you explain how it compares to tDCS, or does it at all, this temporal interference?

Dr. Pascual-Leone: Yes. So this is work that is spearheaded by Neil Grossman (a former Wellcome Trust-MIT postdoc working at MIT and BIDMC, who is now a research fellow at Imperial College London) and Ed Boyden (an associate professor of biological engineering and brain and cognitive sciences at MIT) and myself. And the principle behind it is to use not one pair of electrodes, but instead two pairs of electrodes. Think of it as two channels of passing current into the brain in such a way that a specific time and point in space, those two channels intersect. And in doing that intersection, interact with each other. Now, if one were to just do that, then what may happen is you could end up generating more amount of current at the point of intersection than any other point. And that's sort of the ideas behind things like gamma rays where you can merge together different paths of current, or X ray, and at the point of intersection you get more effect.

In the case of temporal interference, we use an additional little trick, which is that instead of applying direct current that we've been talking about so far, where you build up current to say one million and maintain it at that level at the same phase for a period of time as the direct current. Instead, you can do the same non-invasive stimulation approach but using alternating current. Alternating current flips between positive and negative polarity at a given frequency. So you can apply two channels of alternating current, you can then do so with the phase of the current being opposite. So what will happen is that at a point of intersection between those two channels, they will cancel each

other out, and if you apply the exact same alternating frequency of current in the two channels at the point of intersection, you get nothing. But if you make it so that they differ slightly in their frequencies so that one of them is 2000 hertz and the other one is 2010 hertz, then at the point of interference, there is a cancellation of the 2000, but what is left is the 10 hertz stimulation.

So you can basically, using this trick of the alternating current in antiphase, and intersection between two or more channels, you can deliver a certain amount of alternating current, theoretically, to any one structure in the brain. And that directly makes it possible to target deep brain structures selectively, but non-noninvasively, without the surgery.

I was just going to finish up by saying what we have been able to show so far in the certain paper that you researched is that, when one tries to do that in a mouse, in a very controlled experiment, it actually works and you can selectively modify activity in deep structures like the hippocampus that have to do with memory and so forth. Whether and how well it's going to work in humans, that work is ongoing, and that's the translation from animal models to humans is something that is important to do and needs to be done carefully.

Bill Glovin: Is this the major focus of your lab's research?

Dr. Pascual-Leone: It is one of the major areas. So my lab is focused in the translation of techniques like these, in the development of techniques, and the translation into humans of these techniques to try to help patients with different disorders. And the temporal interference technique is very exciting and is one of the areas we're working on, yes.

Bill Glovin: In the article you write a great deal about brain augmentation products. Can you explain what they are and some of the issues involved in those products?

Dr. Pascual-Leone: Yes. One of the things that has happened is we've learned about this possibility of modifying brain activity, and doing it with specificity for particular activities. Because of the specificity of modifying specific networks, it is appealing to think, "Well, look, I would like to speak better English. I would like to not have an accent. Or I would like to play better tennis, or enjoy different things. And maybe I could do that without impacting the rest of the abilities I have by using modulation techniques that specifically modify activity in given networks." Compare that to taking a medication that washes over the entire brain. So that has opened up a whole amount of hope and fantasy almost in the minds of many people that it might be possible to modify brain activity, and in doing so improve on abilities that we have even beyond normal, hence mending the abilities.

Of course, the first challenge to those approaches or to those thoughts is that the question arises whether it is even possible in the brain to enhance specific functions without having a cost, without losing others. And this is something

that we've thought about and written about before, making the argument that the brain is a net zero sum operation, that if you improve some things, others you lose. That the brain might not be optimizing everything by design to maintain flexibility, and that it might be, "Oh, it's a cost involved." So that's the first concern.

The second concern of this is something that is theoretically possible but doesn't mean that it actually can happen. So it is the case that the studies that have shown, that have tried to improve beyond a certain level, certain abilities, not always works. So what may improve poor performance may not be able to improve good performance into the superior range. Instead, there might be a sort of inverted U shape curve, almost, where if you are very good, trying to get better makes paradoxically things worse. The processes are not the same. So I think there is a hope and the dream of people in augmenting abilities, but a real ethical dilemma to be discussed, and I think that's what we try to address there with this article.

Bill Glovin: It sounds somewhat analogous to gene modification, from a neuro-ethical standpoint. So that'll be very interesting to see how that kind of unravels in the future.

Dr. Pascual-Leone: Yeah, I think that the issues involved are not different from any other approach where the aim is to enhance or to improve on what's normal. So I agree with you that genetic modification and other approaches are similar in the issues that need to be discussed. With the brain stimulation, the way we try to ultimately modify brain activity, if you think about it, is rather artificial. That's not the way that the brain normally works. It's a rather non-physiologic way of imposing a pattern of activity. And because of that, a whole host of other issues could happen through negative ones that need to be discussed and considered and contemplated. And that, by the way, is part of the reason why when you have a technology like tDCS, that is relatively simple, the device can be made at home and then tried, is deceivingly simple in this application. The concern is that people are going to try to "mend abilities" without realizing how complex it always is and how big the potential for a backfire may be.

Bill Glovin: Besides your research, you also work as a clinician. Take us through some of the kinds of patients you'll be treating this week, and what you hope to accomplish.

Dr. Pascual-Leone: So I'm a cognitive neurologist, which is a special area of neurology that has to do with what we call higher cognitive functions and higher brain functions: thinking, memory, speaking, planning. But it also is at a sort of interface between neurology and psychiatry: how we feel and how we act and so forth. I oftentimes will see patients where there's been a loss or there's a concern about losing abilities, often with age. Memory problems, concerns of dementia, these kinds of issues. And in that context, to address brain stimulation, there is obviously the interest of using neurophysiology and brain stimulation techniques to gain insight into what is the actual problem of the patient and to

try to identify strategies to treat it better. So to use them as biomarkers to understand what the underlying problem is.

There is increasingly things we can do with the neurology, and the situation has really changed, even in cognitive neurology, from a situation where it was, at best, clarifying what the problem is kind of approach, and then there was limited things we could offer. The situation now where we can clarify the problem, understand the underlying dysfunction, and actually offer things that can make a real difference in peoples lives, and that's very rewarding.

Bill Glovin: What got you interested in pursuing this line of research?

Dr. Pascual-Leone: Well, I got into medical school, to be honest, because I was fascinated by the brain and the human abilities that we see and hear about, and how that may come about. So I wanted to learn more about it, and I thought going through medical school might be a way to do that. And I was really interested in neuroscience, the behavioral neuroscience or basic neuroscience, per se. What happened to me in medical school is that I also then came to realize that I really enjoy seeing patients, and trying my best to help them is another aspect of my activities. So there's both the scientific curiosity and interest as to how are we or why are we the way we are? And then the honor of the challenge of trying to help patients that struggle. Bringing both together as a clinician scientist in neurology has been an an enormously rewarding adventure, really.

Bill Glovin: Can you tell us a little about your lab and how things are organized?

Dr. Pascual-Leone: I'm happy to. So, as you were mentioning, I direct the Berenson-Allen Center for Noninvasive Brain Stimulation, and it is a division within the Department of Neurology that combines also bridges the Department of Psychiatry, and has in it a number of faculty and principle investigators. Some are neurologists, some are psychiatrists, some are psychologists, neuro-psychologists obviously, scientists. And we try to work in teams, in multi-disciplinary teams addressing various aspects that have to do with using these methods of noninvasive stimulation to both understand the human brain better, in addition to trying to help patients. I think brain stimulation is one of the tools, approaches, that can both help patients while at the same time delivering fundamental insights into the human brain or the brain in general.

Bill Glovin: Does brain stimulation, and particularly tDCS, get the necessary funding that it needs?

Dr. Pascual-Leone: That's a good question. So with the brain initiative, there's been a very concentrated focus on the need to improve on existing technologies to understand the brain, and supporting the improvement of those in developing new ones. So it certainly has been an increasing area of focus, and we've appreciated it enormously. Traditionally, brain physiology and human brain physiology is oftentimes not received, perhaps, the attention that it warrants, in

my mind. But I think that has really changed with the brain initiative, and it's an important and valuable change. It is particularly appealing that is not just NIH, but obviously a number of other institutions and agencies that are a part of the initiative, and with that the emphasis on new technologies across the different realms of publication has also expanded … including the ethics of patients that we were talking about, by the way, have also received increased attention.

Bill Glovin: Is there anything else that I may have left out that you feel is important?

Dr. Pascual-Leone: If I was mentioning the reality of these techniques, of these noninvasive stimulation techniques, is that they have become valuable adjuncts, add-ons to the therapy of patients. For example, tMS, one other brain stimulation technique, there are now four different devices cleared by the FDA for treatment of medication-resistant depression, and the insurance companies are covering the cost, and it's making a real difference in people's lives. There may be 20 patients per day with otherwise treatment-resistant depression, are going into remission. Responding so well that they are no longer depressed. That is really transformative.

So these techniques are making an impact in day to day clinical work, but in addition to that, I think we're only scratching the surface, the tip of the iceberg of these techniques, because of their enormous potential. And the brain initiative is very welcome in supporting that effort, but I think it's continued that for the lasting effort, to really ultimately reach a point where we can really personally the intervention for a given individual to derive the full benefit from these techniques.

Bill Glovin: So that wraps up this month's *Cerebrum* podcast. Many thanks to Dr. Pascual-Leone for joining us, and to his staff for organizing things, both for the podcast and the article. And thank you to the listener for tuning in. Join us next month when we celebrate the 15th anniversary of the Mapping the Field Conference in San Francisco. Our article, "In the Beginning: The First Neuroethics Meeting," will consist of essays by four of the original contributors to that groundbreaking conference. You can also hear these podcasts on SoundCloud, iTunes, Spotify, and YouTube, or at Dana.org. Thank you to the Dana Foundation. I'm Bill Glovin. See you next time.