



# A Compelling Question Drives a Long-Term Passion

## How Do We Develop a Brain Stimulation Method to Improve Cognitive Function in Patients after Serious Brain Injury?

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### Beginning a Journey

I have been immersed in trying to develop a brain stimulation method in the central thalamus to improve cognitive function. I can tell a sequential story of when segments of the work were published, but the research has had an ongoing life of parallel events. The same set of problems has taken me from my initial fascination as an undergraduate researcher through medical school research, my residency—which crystallized my ideas after observing patients—and the stated long-term goal in the first National Institutes of Health (NIH) grant I received, to my work to date.

As an undergraduate, I did historical research at the Montreal Neurological Institute, working with the collected archives of neurosurgeon Wilder Penfield. The institute's director recognized my interest and said, "Not a lot of people are interested in consciousness any more, but there is one neurologist who is still doing it. His name is Fred Plum, and he's at Cornell University." That stuck in my mind. I came to Cornell, and on the first day of medical school at the white coat ceremony, I met Fred Plum (professor emeritus, Neurology and Neuroscience). He has been a mentor ever since.

### Consciousness in the Brain—Acquiring Skill Sets for the Journey

How do some areas of the central part of the upper brain stem and the thalamus participate in establishing and maintaining consciousness in the brain? It is a compelling question. After my third year of medical school at Cornell, I received a Howard Hughes grant, and I focused on absence seizures and the organizational aspects of consciousness in the brain. How can we learn about the circuit mechanisms underlying this type of seizure? I wanted to obtain a new set of skills—to understand how to do mathematical modeling of electrical signals and to think about what the relationship was to consciousness. I went to work on applied mathematics in the lab of Jonathan Victor, now the Fred Plum Professor of Neurology.

After my internship in Chicago, I returned to Cornell to do my residency, during which I figured out a way to take the model I had been pursuing for seizure problems and turn it into a deep brain stimulation question: how might deep brain stimulation modulate perceptual function?

I began writing grant proposals to fund the research that could be the foundation for setting up models to develop new therapeutics. Fred Plum, however, made another recommendation, saying, "This





## Fascinating!

- This patient showed absolutely no evidence of awareness of anybody. But every now and then the patient would blurt out a single word, usually an expletive in one of two languages, and it did not appear to be related to anything.
- A sentence, not a word, is the unit of meaning in language. A word could be like a reflex, given that one can speak so much faster than one can think.
- We found that turning on the brain stimulator, at first gradually and then effectively, restored spoken language, the ability to eat, and the ability to control muscles and to move.
- We can take a few cases and go through this process thoroughly ... to understand how the patient's brain changes, how their behavior changes, how the patient changes, and how the family changes.

is great, but I don't want you to work only in the lab. I have another project I'm trying to get started. I'm working with Rodolfo Llinás downtown at New York University (NYU) with magnetoencephalographic technology, and I want to restart a program that we worked on in the mid-'80s. I want you to come and work with me on that, as well."

a vegetative state, but every now and then would say single words. I said, "Wait a second, that can't happen. That's not the way it works—you don't say words if you're in a vegetative state!" We examined the patient, got the history, and talked to the family. They were very clear—this patient showed absolutely no evidence of awareness of anybody. But every now and

If we knew a patient was able to talk every now and then, perhaps we could get the patient into that state and hold the brain in that state. But could we get the brain to function in that state?

Plum and I evaluated patients in nursing facilities and other places throughout the tri-state area. It was one of the most interesting periods in my training.

Tough on teaching and pursuing funding, Plum said, "You must know how you're getting funded. You should write your NIH grant as soon as you have preliminary data." I wrote at least six grants my first year as a senior resident. As I finished my residency, I was funded with grants and the conceptualizations of two concurrent post-docs. Working with Victor, I got preliminary data and wrote my first NIH grant seven months out of residency. And I got it! It was a training grant that set me on a path.

### "Words without Mind"

We went back and examined patients in the chronic vegetative state. We reestablished an earlier benchmark created in Plum's lab—the first evidence that the vegetative brain functioned at such a low level, 30 percent of normal function, and that it was apparently anaesthetized based on a resting metabolism—and correlated it with the new technologies. We worked, particularly with Llinás at NYU using magnetoencephalography, technology that measures magnetic signals in the brain. As Plum and Llinás joined forces, I became the point person for the study.

We eventually enrolled patients in the trial. The first patient we studied had been coming to the clinic every day for about 20 years. The patient was known to be in

then the patient would blurt out a single word, usually an expletive in one of two languages, and it did not appear to be related to anything.

It was a remarkable case, an unusual story of a patient who had an abnormality of blood vessels in the center of the brain. Over a two- to three-year period, the blood clot had continuously ruptured and destroyed almost the entire brain. The parts of the brain that it had not destroyed were like a little model of the human language system— islands that preserved the expressive language, cortical regions, the underlying parts of the basal ganglia, and some very small part of the thalamus that we could not identify anatomically or metabolically. We knew these parts were still there because we could identify them using magnetoencephalography, which showed us that a signal was going to the right part of the brain in the auditory regions.

This became our first insight that had not been established in the literature into the existence of modular preservation, islands of functions—even where there is almost no brain remaining—that could produce a clinically visible feature, a fragment of behavior. In this case the fragment of behavior was a word. A sentence, not a word, is the unit of meaning in language. A word could be like a reflex, given that one can speak so much faster than one can think. We concluded in a paper—"Words without Mind," by Rodolfo Llinás, Urs Ribary, Fred Plum, and me—that what we were looking at was a modular

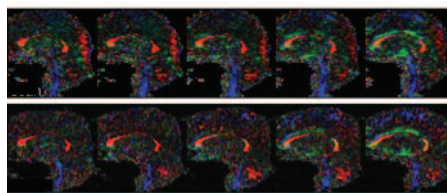




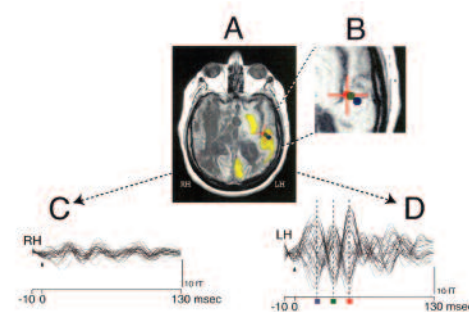








Longitudinal measurements of regional fractional anisotropy over an 18-month interval following late recovery from MCS



We interpreted our results as evidence that structural reconnection of existing cells over time in a severely injured brain is possible.

circuit that, lacking motor fixed-action patterns, produced words almost like a reflex. We saw how the first level up from the vegetative state with no evidence of cortical activity might look.

#### On the Trail

As we studied other patients, we found more examples like the word reflex case, but nothing as dramatic. A concordance among the measurements we made with PET scanners, magnetoencephalography, and structural imaging gave us a systematic way to study it. Brains can be wiped out or almost wiped out. We began to see that there might be fragments of behavior attached to them, which led to another question: what about the many people who were not in the vegetative state, but their level of function ranged from barely doing anything to being conversant? And this led me to the brain stimulation work.

If we were to target patients for brain stimulation, these were the kinds of patients we might be able to stabilize in their best level of function. If we knew a patient was able to talk every now and then, perhaps we could get the patient into that state and hold the brain in that state. But could we get the brain to function in that state?

#### Play It Forward, Play It Backward

The first study I conducted after the vegetative work was to look at two patients with minimal levels of behavior. These patients were not in the vegetative state, but they could do no more than follow a command

inconsistently; we could not communicate with them. We took them through the protocol of our previous study, but added a study of functional magnetic resonance imaging in collaboration with Joy Hirsch (then at Memorial Sloan Kettering, now at Columbia University), using a paradigm the Hirsch lab had developed for anesthetized babies. We played spoken language—narratives read by relatives the patients knew well. Then we turned around the narratives, recorded in digital audio, backwards in time so that they could not be understood.

Data showed that normal subjects activated not only the same areas of the brain to both stimuli (forward and backward) when they listened to each version, but they activated these areas more strongly when they were presented with the stimulus they could not understand—as if they were listening more carefully in order to understand. The patients activated the same auditory and language areas. In one case we saw almost the entire language system; it looked very normal. But when we turned the narrative around in time, activity shut down dramatically compared to the normal subjects. It was as if the patients alerted to the familiar voice and engaged with it. We could not judge that from the scan, but they certainly activated this network in both halves of the brain and in all the relevant areas of the brain.

One of these patients became the first brain stimulation subject four years later. We studied this patient because the patient fit the profile—injuries to the central structures

of the brain and inconsistent responses. We obtained data that showed a robust language system in this brain, even though it did not seem to be working properly. Wow! What had been occurring in the brain with these measurements was not transparent, and the findings raised more questions than they answered.

### A Miracle Man and Cutting-Edge Research at Cornell

As the work with that patient continued to evolve, we had an opportunity to study a case that came to public attention in 2003. A man in Arkansas, Terry Wallis, began to speak fluently on his own for the first time in 19 years. One day his mother walked into the nursing home, and the nurse said as she did every day, “Who’s that?” And he said, “Mom.” Everyone was stunned—he had been silent for 19 years.

About eight months after his spontaneous recovery, which was widely reported in the world press, we got a chance to study him. We did the whole series of imaging studies—PET studies, EEG (electroencephalography), and we added a new study.

At the time, Henning Voss, a MR physicist at Cornell, had been working on diffusion tensor imaging, a modality of MRI. Diffusion tensor imaging enables a measurement of how water molecules move in the applied magnetic field. Instead of pursuing the interpretive aspect of this technique that involves using algorithms to create pictures of the fiber connections in the brain, we focused on the actual MRI signal, which comes in a three-dimensional volume. We quantitatively assessed the measured water movement in three principal directions for each volume. This allowed us a way of doing very precise quantitative structural brain assessments. We were able to assess the extent of the injury in the man who recovered after 19 years.

We were able to show unambiguously that the patient’s brain was overwhelmingly damaged when we qualitatively and quantitatively compared his brain to normal subjects. He had the worst grade of diffuse axonal injury. When Voss and I sent the findings to be published, we received comments that said, “This is real interesting, but we want to see

another patient to determine whether or not this might occur in other patients.” When we published the study, it made the front page of the *New York Times* (as did our fMRI study).

### The Miracle Man Improves Further

Around the time we brought in another patient to study who also had very unusual changes many years after severe brain injury, we were also able to study Wallis

We licensed this portfolio into a startup company, called intElect Medical Inc., which is partly owned by Cornell and mostly owned by the Cleveland Clinic.

again. He had improved. He was gaining more control of his articulation and speech. His ability to form new memory, which had been nearly absent, was beginning to show changes. He was also starting to move his lower limbs, which we thought would be permanently paralyzed. When we repeated his images, we saw that the areas in the brain that had shown increased connection were still changing while measurements in most other areas in his brain were stable. We also saw new changes in another area related to a motor control system—a quantitative result. We interpreted our results as evidence that structural reconnection of existing cells over time in a severely injured brain is possible.

At the same time of our finding, a prospective study appeared in the journal *Brain*. It included 30 patients with severe brain injury who were studied over a one-year period showing very similar results to ours. Researchers discovered that in a cohort of these patients who were improving, brain areas showed recovery of the same diffusion tensor imaging measures, and some patients, like Wallis, actually recovered to values above normal.

### A Story of Parallel Projects

I worked with ideas about how these structures in the center of the brain might be doing their jobs. History told us that these cells activate during wakefulness and had something to do with consciousness in turning the brain on. But what were these areas of the brain doing during the time

they were most active? They must be doing something. I searched the literature for characterizations of the cells in this part of the brain to give us insight into variations in their activities during a wakeful state. I found two fascinating papers that had been done in the early 1980s showing that these cells in the part of the brain associated with activation and arousal played a role in eye movements.

Keith Purpura, a visual neurophysiologist at Cornell, had been working on how visual information was partitioned and the role of the eye movement as a signal to the visual cortex. Purpura and I began a discussion that nearly immediately led to a published theoretical paper, which became the kernel of my second NIH application—to develop an animal model to test our theory.

At the same time, I worked with Plum to develop a program where we could do brain stimulation in humans. I also worked with Ali Rezai, who had returned to New York after a fellowship in brain stimulation and was set to establish the brain stimulation program at the hospital for joint disease in the Manhattan veterans administration. Our effort to get a VA grant to do brain stimulation in 1998 began a seven-year process of grant rejections, with split reviews ranging from “the best proposal I have ever read” to “deep brain stimulation would never play a role in dramatic brain injury.” But the work of putting together ideas for grants led to a more precise formulation about how to set up a strategy for doing the brain stimulation.

Back in 1995 when we could not identify a source of funding to do the work, I had thought about the companies that made the brain stimulation units and contacted the Medtronic Corporation. I was warned, however, to get a nondisclosure agreement. So, I worked with CRF (now the Cornell Center for Technology, Enterprise, and Commercialization, or CCTEC) for a year



and a half and was asked by CRF to write a disclosure to protect the intellectual property (IP). Cornell applied in 1997 for a patent issued in 1999.

In 1997 I had begun a collaboration with Joseph Fins, Medicine/Public Health/Ethics, which was incredibly important as we recast our approach with a focus on where it would be most ethical to apply brain stimulation. The team—Plum, Rezai, Victor, Purpura, Fins, and I—physically went to the NIH to try to get funding for both the basic and clinical work. After long meetings with the program officer and, later, rejected grant resubmissions, the program officer finally said, “Well, you just can’t submit this grant until you do it.”

During the same time, the director of the NIH National Institute for Child Health and Human Development, which has its own subcommittee on brain injury, contacted me and said, “We have a request for grants going out, but it disallows surgical costs. However, you could write a planning grant.” We got an easily fundable score for the planning grant, but the same grant with the surgical budget submitted to the traditional review panel had received an insanely high (poor) score. The only way to do the surgical work, which brings us to 2002–3, was to find a way to capitalize it ourselves.

### Licensing the IP

In 2003 Cornell began negotiations with the Cleveland Clinic, which was founding a company around the technology they had developed for brain stimulation tools, methods, and systems. They were interested in our patent portfolio, which now included a series of patents. We licensed this portfolio into a startup company, called intElect Medical Inc., which is partly owned by Cornell and mostly owned by the Cleveland Clinic. The Cleveland Clinic used gap funding to develop their own technology. Cornell agreed to license these patents and principles to the Cleveland Clinic, and the Cleveland Clinic put up the seed capital to do the first surgery. This is how we were able to start the trial. Cornell and Cleveland then partnered with the JFK Johnson Rehabilitation Center and Joseph Giacino, a neuropsychologist and expert in quantitative behavioral

assessments of patients with limited ranges of behavior.

### How the Brain Stimulation Trial Worked

For the study, I wanted to get the patient with inconsistent eye-movement communication and language responsive networks in the brain we had studied in 2001 (published in the 2005 paper). The patient had been in a nursing home several years prior to the approval of the study. When we brought the patient back to JFK Johnson Rehabilitation Center, which had become the site for the trial, the patient was measured to be in the same condition as four years earlier, and therefore fit the profile for the study. There was a four-month period of reentry into rehabilitation, getting healthy and recovering from various problems, and then off to surgery.

We had a two-month period when the brain stimulators were not on. We compared the behavioral data of the on and off states. We had a five-month period of adjustment of the deep brain stimulation, during which many things improved, and a six-month period in a trial in which every 30 days the patient was on and off the stimulation and blinded evaluations were obtained. Over this period of 11 months when the patient was exposed to brain stimulation, compared to the earlier six months of measurements when the patient was not exposed to brain stimulation, we found that turning on the brain stimulator, at first gradually and then effectively, restored spoken language, the ability to eat, and the ability to control muscles and to move.

### What Is a Brain Stimulator?

A brain stimulator is like a cardiac pacemaker—an electrode that goes into the brain tissue and delivers an electrical current. It turns on and off, and we in this particular trial turned it on and off at 100 cycles per second (hertz). One of the reasons we did this is because my collaborator, Dan Hererra, Psychiatry, developed a study in rodents on brain stimulation looking at the effects of gene expression and behavior. We found that if we stimulated this part of the thalamus at 100 hertz, memory function in normal rats improved when we turned on the stimulator.



Back row: [l. to r.] Keith Purpura PhD, Neurology and Neuroscience; Daniel Herrera MD/PhD, Psychiatry; Renee Kahn RN, Nursing Staff Citigroup Biomedical Imaging Center; Jennifer Hersh MA, Public Health; Erik Kobylarz MD/PhD, Neurology and Neuroscience

Front row: Stanley Goldsmith MD, Nuclear Medicine; Schiff; Joseph Fins MD, Medicine/Public Health/Medical Ethics; Shankar Vallabhajosula PhD, Nuclear Medicine

## About Schiff

**Years as Cornell faculty**  
11

**Came to Cornell from**  
Stanford University

**Favorite spot on campus**  
A seven-block radius around Weill Cornell Medical College in New York City

**Cornell's research distinction**  
Collaborative environment

**Cornell's trademark**  
A legacy of unique talent

**I am also**  
A hobbyist dropout







### Now That We Know We Can Actually Do This ...

We have a lot of work to do. We and hundreds of other people could work on this for at least the rest of my career or a lifetime—figuring out the details will take a long time. How much of the how and the why of brain stimulation do we know? We have increasingly better ideas about how it works. And the “whys” that we propose make sense: the geometry of the cell connections to and from the area we stimulate makes these cells vulnerable to any process that causes a lot of neuronal death in the brain. Their main anatomical specialization is that they are connected to very wide areas of the brain, and they have an important functional capacity to maintain activity that allows us to hold a behavioral set—to focus attention, allocate attention over time, or keep things in our working memory.

These neurons are the most vulnerable to multifocal injury. Part of what happens after a severe injury is that, although these cells may continue to play a key role in maintaining these functions, they do it poorly. This is in part why people with severe brain injury are cognitively slow. They have problems being attentive, remembering things, and acting in the world and remembering what they are doing. At this stage of the technology, we put electrodes in the thalamus, turn them on, and leave them on. The brain cannot learn anything intrinsically from the signal we give it. But it can override the output of the cells so that they keep target areas in different parts of the brain active enough to better maintain the remaining processes that allow memory, attention, and the ability to sustain a task. This is how we think it works.

It turns out that, if we keep the brain stimulator on for a while, even if we turn it off, the person does not go back to the previous state. Changes are occurring in the brain that are like learning and memory, like the natural recovery process associated with this. The process to figure out the biology of this aspect of our findings will be long. When we think about how this will work out as a scientifically based method in the future, it will be not only about electrical stimulation, but also about the biology of the response.

### Next Directions

What's next? We have two major directions: one is to understand more and in finer detail why the brain stimulation does what it does. We can work with the tools we have, but we also need to develop new tools. We want to know better how to assay circuit responses. Victor is returning to do a mathematical analysis of the EEG, and we have gotten a grant together. Part of the grant

To develop insights into human problems presented by disease, to understand their mechanisms, or to develop new treatments are the top three goals one could have as a biomedical scientist.

will develop a center—at Rockefeller and Cornell—for the study of long-term recovery. Fins and I will codirect the center and look not just at the scientific aspect of the recovery of consciousness, but also at needs of the families and patients and potential goals.

We are setting up a project to study long-term recovery following severe injury in which we look at the scientific biomarkers aiming to understand the circuit mechanisms and how the brain evolves its recovery pattern. Very importantly, we try to understand carefully what happens as patients recover and the impact on their caregivers and families. These are very tough problems. Sometimes we will find patients who make amazing recoveries, and everyone is gratified by it. Most of the time, we will find in-between cases. We need to understand the goals of care. What is achievable? What is not achievable? How do we communicate information? How do we communicate uncertainty? How do we help guide people, and how do we learn from their experiences?

Fins and his research staff interview and compile data on the families of our study subjects. We hope to have a routine where we can take a few cases and go through this process thoroughly day by day, month by month, over a year's time to understand how the patient's brain changes, how their behavior changes, how the patient changes, and how the family changes. We will build

a comprehensive database for understanding how to handle this difficult area of medicine.

### Fallen Hobbies

I have hobbies that I have not been able to do for a while, but right now, I am raising my two children. Running, karate, and reading outside my work are among my fallen hobbies. I have little time for anything except work and family.

### The Last Word

#### Only a Few Special Places

To develop insights into human problems presented by disease, to understand their mechanisms, or to develop new treatments are the top three goals one could have as a biomedical scientist. To do this kind of work requires a very special environment. The word translational is thrown around a lot, but it is not easy to achieve. Having a top-flight academic medical center in a city with one of the largest populations in the world and access to science and medicine with ease is rare. And because we do systems science, which combines biology with imaging research, theoretical research, mathematics, and physics, vast opportunities for collaborative research with the Ithaca Cornell faculty are yet to be realized.

#### For more information:

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