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RebrAIn Simplifies Precision Targeting for Parkinson's Disease

Deep brain stimulation is the most effective treatment for movement disorders associated with PD, but it comes with a complexity that limits access to the surgery. RebrAIn is providing an AI-enabled service that helps neurosurgeons more precisely localize the therapy target, potentially making procedures faster, safer, less costly, and more widely available.

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▶ MARY STUART

For Parkinson's disease, deep brain stimulation (DBS) is far more effective and safer than drugs for managing the condition's motor symptoms. DBS, like any therapy addressing a particular biological target, is most effective and tolerable when it hits the mark. To address the movement disorders that affect patients with Parkinson's disease (PD) and essential tremor, DBS needs to stop the problematic signals coming from the ventral intermediate nucleus (VIM) in the subthalamus region of the brain, which requires placing stimulation leads with an accuracy of one millimeter or less from the target.

But finding the X that marks the spot is no easy task with today's technologies, and inaccurate lead placement is one of the top factors responsible for suboptimal outcomes. At best, the reported efficacy of 60-80% for DBS in these patients still leaves room for improvement.

With the help of artificial intelligence, **RebrAIn** (Pessac, France and Newark, DE) has developed a service that provides neurosurgeons with the information they need for accurate lead placement imminently before the surgery. The start-up's software as a service model suits the demands of the busy operating suite, "which doesn't need another computer or box," notes David Caumartin, the company's CEO.

With more than 25 years of executive experience, at both start-ups and multinationals, Caumartin officially became CEO in January of this year. He joined scientific co-founders Emmanuel Cluny, chief medical officer and president of the board, and a professor of neurosurgery at Bordeaux University Hospital, where he heads up the neuromodulation division, and Nejib Zemzemi, chief scientific officer and chief technology officer, a researcher and expert in mathematical modeling and machine learning at INRIA (National Institute for Research in Digital Science and Technology) at the University of Bordeaux.

Caumartin explains that today, the use of multiple modalities for identifying the desired target in the subthalamus region adds cost and additional risk to procedures. With RebrAIn's technology, a user simply uploads a standard preoperative MRI image to the RebrAIn cloud platform, and the company's algorithm sends back a 3D annotated model of the brain, marked with the precise spot for lead placement (or ablation, in future applications). Clinicians can plan their surgical approach by interacting with the models, displaying, reviewing, annotating, and exporting data for analysis.

RebrAIn's founders have been quietly advancing the company's platform, called *OptimMRI*, for several years with the support of nondilutive research grants. The start-up recently raised its profile with the announcement in March of a €3.7 million seed round led by Karista, an early-stage investor with a focus on digital health, with the participation of Nouvelle Aquitaine Co-Investissement, a

private equity firm in Bordeaux, France, with a regional focus.

With great capital efficiency, RebrAIn has already helped clinicians in France treat more than 450 patients with *OptimMRI*, and in June 2023 the decision-support tool gained 510(k) clearance from the FDA. The company is now focused on creating awareness of this new service for neurosurgery, a process Caumartin describes as evangelizing the market. "We are looking to identify our key opinion leaders—our 12 apostles—who will duplicate what we have done in France, Italy, and Spain, and then go as quickly as possible to the US."

Toward an Effective and Reproducible Therapy

Cuny and Zemzemi set out to solve two essential technical challenges facing brain neuromodulation for PD. The first is the difficulty of identifying, in a timely manner, the precise therapeutic target on a patient's brain. This is challenging to do intraoperatively, and because the brain moves, preoperative measures must be efficient and speedy. The solution would also address the second challenge: the inconsistency of results from one deep brain stimulation center to another.

All DBS procedures begin with preoperative MRI, usually low-field (generally 1.5T-3T) MRI, which doesn't present clear visual landmarks for the location of the VIM. Clinicians calculate the location of the VIM based on formulas using coordinates and distances from visual landmarks. But since no two people have the same brain anatomy, this indirect method is flawed from the get-go. (One might see the target directly with high field strength [7T] MRI, but this is not available or practical in most settings.)

To increase the accuracy of targeting, a second step of microelectrode recording (MER) of the brain has been adopted by many centers that offer deep brain stimulation. Using a fine microelectrode wire to measure along a path to the hypothetical target, MER can find the VIM by its unique pattern of electrical activity. Patients under local anesthesia are awake during this procedure and can supply additional information by responding to the electrical impulses delivered during the recording session. Various studies have indicated that the target locations identified by MRI and MER don't match as much as 20% of the time, so having two sources of information is beneficial.

> "We found a less than one millimeter difference between what our algorithm was predicting and what was actually found under an MRI-guided procedure."
>
> —David Caumartin

The drawbacks of MER include the time and cost of placing a patient under local anesthesia to conduct an additional presurgical step, the discomfort of the patient (not pain so much as anxiety), and possible adverse events from the recording procedure including intracerebral hemorrhage. Says Caumartin, "It is a complex electrophysiology brain exercise, requiring not only the neurosurgeon, but also the neurologist specializing in electrophysiology, inside the OR, adding people, staff, complexity, and cost to procedures, just to be able to reach the gold standard of a 60% tremor reduction, either on the scale of essential tremor or Parkinson's disease."

In search of a safer and more effective way to give neurosurgeons the guidance they need, RebrAIn's founders decided to reverse engineer the problem. Using as inputs good clinical outcomes of 60% tremor reduction or better in Parkinson's and essential tremor patients after DBS, preoperative images, microelectrode recordings, and postoperative imaging (standard 1.5T MRI) from which the coordinates of the active contacts and 18 anatomical landmarks were extracted, the researchers used machine-learning regression to build prediction models. Caumartin states, "We found a less than one millimeter difference between what our algorithm was predicting and what was actually found under an MRI-guided procedure, and that was enough to get RebrAIn a CE mark and an FDA clearance" for *OptimMRI* as decision-support software that aids neurosurgeons.

Improving Access With a Simpler and Less Costly Procedure

According to Parkinsons.org, there are 10 million people with the disease worldwide (1 million in the US, with 90,000 new diagnoses each year). It is the second most prevalent neurodegenerative condition after Alzheimer's disease, and it is expected to surpass the latter in coming years.

About 1.6-4.5% of PD patients are candidates for deep brain stimulation, due to the lack of efficacy or complications of drugs, but only a fraction of eligible patients receive the therapy because of high cost, complication rates that vary from center to center, and patients' fear of living with "a brain pacemaker" for the rest of their lives. Essential tremor is an even larger population; about 5% of people over the age of 60 suffer from this movement disorder.

RebrAIn believes *OptimMRI* will address all those hurdles. Although as with any new technology, clinicians will initially use *OptimMRI* as an adjunct to the standard of care until they're comfortable with the information it provides, ultimately, Caumartin believes neurosurgeons will be able to do without MER, which would improve the cost, speed, and risk profile of procedures. As noted, MER adds time and cost in a couple of ways; it requires additional staff—a neuroelectrophysiologist in addition to a neurosurgeon, and for the patient to undergo local anesthesia during awake brain electrophysiology recording. Patients would prefer to simply undergo the general anesthesia required for the implantation of the deep brain stimulation hardware.

To collect the appropriate medical economic data, the company is conducting a large randomized, controlled Phase III trial, enrolling 130 patients at 10 sites in France. Patients will be enrolled to either the standard of care, which includes the microelectrode recording step, or target localization by *OptimMRI* only. Caumartin expects the trial to be completed by July. Prior to the Phase III study, the start-up collected cost data on a small number of patients, soon to be published. He reports, "We saw a time reduction of about 50% from six hours and 15 minutes to three hours and 15 minutes, with three fewer days of hospitalization. We save Bordeaux hospitals about €10,000 [about $10,850], and we expect to save even more in the US, where the procedure is more expensive." The CEO adds that the time savings might even allow hospitals to increase the number of patients they treat, from a throughput standpoint.

Finally, *OptimMRI* is a tool that will be even more compelling when Parkinson's disease is treated by irreversible ablation, rather than neuromodulation of the target. RebrAIn is looking to next apply its platform to the treatment of PD by high-intensity focused ultrasound (HIFU). "HIFU is about five times cheaper than a neurosurgery suite," states Caumartin. "In the US, reimbursement for tremor treatments is about $30,000 to $50,000 with HIFU, whereas DBS costs $100,000 to $150,000." HIFU offers a shorter procedure, he continues, and is ambulatory. "I have personally seen patients arrive in the morning and leave in the afternoon. They can drink coffee again [without tremor], which is a profoundly felt improvement." Prior to the procedure, many can't walk, and they are immediately transformed by the HIFU procedure, he says.

RebrAIn is now preparing to launch its product in France. "We want to control the launch ourselves in the DBS market, because we want to make sure hospitals understand the economics, the business models, and the product definition. Once we are in 20-30 sites, we will be open to discussions on distribution and licensing." MTS

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