MedTech STRATEGIST

An Israeli Medical Device Accelerator in Wartime

Wendy Diller

Ignored No More: MTI Start-Ups Address Longstanding Needs in Women's Health

Colin Miller

Alzheimer's Disease: Can Machine Learning Fix a Broken Brain Network?

Mary Stuart

AS COMPETITIVE LANDSCAPE SHIFTS DIABETES COMPANIES JOCKEY FOR POSITION

Mary Thompson

Alzheimer's Disease:
Can Machine Learning Fix a Broken Brain Network?

Sinaptica began its commercial journey only recently, although its deep scientific underpinnings have already gotten it through a positive Phase II trial, which dramatically showed the benefit of a noninvasive neuromodulation therapy designed to achieve a network effect that slows disease progression in patients with mild to moderate Alzheimer's.

▶ **Mary Stuart**

The pathophysiology of Alzheimer's disease is not well understood; and that's perhaps why more than 200 drugs under investigation for this degenerative brain condition have failed in the last decade. Plaques made of amyloid-beta and tangles of insoluble tau proteins are two physical manifestations of the disease, but it's not known whether they're at the root of the disease, or covariants with some other disease-causing factors.

The founders of **Sinaptica Therapeutics** thus decided to take a very different approach to Alzheimer's by identifying the electrical network that's faulty in AD patients, whether that dysfunction starts with amyloid plaques and tau tangles or not, and then noninvasively stimulating it back into harmony. That's a simplistic explanation of the company's therapy, which so far appears to work, at least according to a 50-patient Phase II trial published in Brain in November 2022.

Over 24 weeks, 50 patients with mild to moderate Alzheimer's disease were randomized to either the new experimental neuromodulation therapy, involving personalized repetitive transcranial magnetic stimulation (rTMS) that is targeted using EEG and MRI and noninvasively delivered to the default mode network of the brain, in combination with optional standard-of-care pharmaceuticals (acetylcholinesterase inhibitors), or to drugs plus a sham rTMS procedure.

On four key measures—dementia (CDR-SB), cognitive status (ADAS—Cog and MMSE), and activities of daily living (ADCS-ADL)—the patients receiving the personalized neuromodulation saw pronounced slowing of progression, whereas the patients in the sham arm experienced significant decline. Based on the Phase II results, Sinaptica was founded to develop and commercialize the therapy, currently called *SinaptiStim*, and following publication of the Phase II data, the FDA awarded Sinaptica its Breakthrough Device designation.

These results are unprecedented, according to Ken Mariash, who joined the company as CEO in March 2023 to marshal the resources to move the product through clinical trials and to market. "In patients who are rapidly declining, we slowed decline by more than 80% across four cognitive and functional endpoints, which is phenomenal. We also have electrophysiology data that shows we are preserving the cortical excitability of the brain, preserving the brain's signaling." The company also collected imaging data that shows preservation of the volume and morphology of the gray matter in patients in the treatment arm, whereas cortical morphology degrades in those in the sham.

Mariash, a veteran of the neuromodulation industry as the former head of strategy for Boston Scientific's neuromodulation business who ran Cosman Medical for four years after its acquisition by the strategic. Now he's preparing Sinaptica for a Phase III trial, which involves getting the right hardware partner (done; an undisclosed agreement is in place, he says), sourcing 64-channel EEG, and hiring the right CRO to execute the Phase III design. Sinaptica's early backers include Time Zero Capital, Sony Innovation Fund, The Daly Family, Wilson Sonsini Ventures, HealthTech Capital, and other angel investors.

In a field that sees little or slow progress, it seems this new company burst on the scene out of nowhere, but its scientific founders have been working together on the science behind *SinaptiStim* for at least nine years. Scientific co-founder Giacomo Koch, MD, PhD, professor of physiology at the University of Ferrara and director of the Brain Stimulation Laboratory at the Santa Lucia Foundation, in Rome, Italy, has treated many patients with dementia. Working from Boston, Emiliano Santarnecchi, PhD, PhD, associate professor at Harvard Medical School and director, Precision Neuroscience and Neuromodulation Program at MGH, is an expert in signal processing and biomarkers. It was company president Richard Macary, an entrepreneur with decades of experience as a corporate consultant, advisor, and analyst within the finance, technology, consumer, biotech, and medical devices industries, who saw the opportunity to build a company around their groundbreaking research.

Speaking Brainish

Going into it, the founding team had a few "knowns" in brain research to work with: that the default mode network (DMN) is broken in Alzheimer's disease; that one of the main hubs of the default mode network, which encompasses

distributed and interconnected brain regions, is largely centrally accessible via the precuneus section of the brain; and that it is possible to create biomarkers of brain activity by using transcranial magnetic stimulation and EEG to respectively perturb and measure the propagation of single pulses throughout the DMN.

To tackle a disease of cognition and memory, Koch and Santarnecchi took a machine learning approach, recruiting, between 2014 and 2020, patients with Alzheimer's disease, other types of dementia, and healthy controls.

After performing TMS-EEG studies on subjects (stimulation of the brain and its evoked response), the team extracted some 70 different features and developed algorithms to match them to the presence and progression of Alzheimer's disease. Mariash says, "We are lucky to have access to the largest database of TMS EEG data on the planet—hundreds of patients over time. It is a longitudinal database created by our scientific co-founders. It follows patients with Alzheimer's disease as well as healthy patients."

It's a deep tech approach, and Mariash, the businessman, jokes, "They are helping us learn how to speak brainish," that is, how to understand the signals that show when you've stimulated the right network, and whether or not that network is dysfunctional. "A lot of companies throw around the terms AI and machine learning, but our scientific co-founders just published a paper [by Tautan et al., in *Scientific Reports*] on using random forest modeling to look for perturbation biomarkers in the brain."

That was the foundation for developing a therapy that could reignite connections in a faulty default mode network in a patient with Alzheimer's disease. Mariash points out that the company's neuromodulation therapy is different

from conventional transcranial magnetic stimulation in three ways: first, it is initially personalized and subsequently recalibrated to make sure it maintains the right program for that patient. "Each patient's brain, and their response to stimulation, is different, and over time, the brain changes, especially in Alzheimer's disease patients." Second, the company isn't just stimulating a nerve, it's lighting up an entire network. "Getting confirmation that we are hitting all the individual nodes of the default mode network is critical." Calibration occurs by TMS, EEG, and MRI. "It involves gigabytes of data that need to be interpreted by our algorithms to personalize the therapy and to recalibrate it," notes Mariash.

And the third aspect that distinguishes *SinaptiStim* from "old school" TMS is neuronavigation. "We load a patient's MRI into the system so we know where we are going in 3D space. To do this therapy reproducibly and safely, we need to stimulate the right area. If we move just a little bit out of range, we might hit the wrong network." With neuronavigation, the clinicians can aim the therapy to the same place with precision and reproducibility. Mariash contends, "TMS-EEG is an amazing tool for knowing that you hit the right network."

Not in Competition With Drugs

There are many steps involved in the *SinaptiStim* therapy, which takes place in a clinic. Patients first come in for an MRI and a calibration session. The clinician precisely places a 64-channel EEG cap on the patient's head and pairs it with TMS. The clinician also registers the patient in the neuronavigation system using a digital pen, which in 3D space indicates where the patient's brain is and automatically identifies large structures in the brain, including where the precuneus should be.

Then, calibration (the company calls it "the MAINTAIN protocol") begins. The

clinician stimulates different regions of the precuneus with TMS-EEG, which records the response. The patient is then sent home while the collected data is processed in the cloud within hours. The output is a set of coordinates that tells the machine where to stimulate, as well as the stimulation parameters for that patient, for example, amplitude.

Once that is accomplished, the patient comes back for two weeks of daily 25-minute sessions, Monday through Friday, during which 1,600 pulses are delivered per session. This is the induction phase, designed to kickstart the brain. The therapy is thereafter reduced to a once-weekly session lasting 25 minutes. Every few months, the technician will recalibrate the therapy to ensure maximum engagement.

In theory, this sounds like an expensive and complicated therapy, compared with drugs, if there even were any disease-modifying agents effective against mild to moderate AD. One drug recently entered the market, but for mild cognitive impairment or mild dementia only, the population that was studied in the treatment's clinical trials. July 2023 marked the FDA approval of *Leqembi* (lecanemab), the first Alzheimer's drug to demonstrate that it slows the progression of the disease (although there's controversy in the field around how much change is clinically meaningful.) It's not the ultimate solution; developed jointly by **Biogen** and **Eisai**, *Leqembi*'s approval also came with a boxed warning about the potential for brain bleeding and swelling, and the drug's labeling directs periodic monitoring by MRI to watch for clinically severe symptoms that would call for discontinuation of the drug, which is a hidden cost. More obvious is the high price tag of one year of *Leqembi,* estimated to be $26,500. And finally, it is administered by in-clinic 90-minute infusions sessions every other week, which is another cost.

On the other hand, at least according to the Phase II study, *SinaptiStim* is an extremely safe, noninvasive therapy. Says Mariash, "When you actually total all the related costs of these new drugs, I think we can provide a very cost-effective first-line therapy in comparison."

But it won't be either/or for a complicated disease like Alzheimer's. "This is like cancer, or HIV. It's going to require multiple therapies," he points out. The Phase III trial of donanemab (**Eli Lilly**) recently demonstrated that in early stages of Alzheimer's, it can significantly slow down cognitive and functional decline. "In a world where drugs like donanemab can clear amyloid and the patient then stops taking the drugs, what will they do next?" asks Mariash. With a safe and noninvasive therapy, he believes *SinaptiStim* could be the next logical step, but it will also most likely work well in combination with drugs.

"As we go forward, we will continue to learn how to optimize the therapy. Maybe one patient should get a particular waveform. There are so many ways to optimize because every time we stimulate a patient, we learn so much," Mariash says, which is not the case for a drug infused into the arm.

SinaptiStim will be constantly adapted to a patient's changing needs, and over time, "neuromodulation might actually get to the root of the problem, which might be oscillatory imbalances, synaptic dysfunction, and network dysregulation," says Mariash, pointing out that the Alzheimer's brain exhibits epileptiform activity, that is, faulty signaling. "If we can stabilize misfiring in the brain and enhance cortical plasticity, we might get to the root of the pathology."

Posted on MyStrategist.com Nov. 21, 2023