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It's not just about plaques: rTMS also reduces cognitive and functional decline in Alzheimer's

By Annette Boyle, Staff Writer

The growing number of drugs gaining U.S. FDA approval for Alzheimer's disease has kept their ability to reduce amyloid beta and tau proteins in the news, but the degenerative disease is not simply a matter of tangles and deposits. A loss of synaptic plasticity and disrupted neural networks underlie the signature impairment of memory and cognition – and those, researchers showed in a recent study in *Brain*, can be strengthened by non-invasive stimulation that addresses the brain's electrical dysfunction.

"The brain is very much an electrical organ," Sinaptica Therapeutics Inc. CEO Ken Mariash told *BioWorld*.

Sinaptica is banking on being able to manipulate the brain's electrical signals to preserve its health and full capabilities. And, based on the *Brain* results, it appears to be more effective than drugs in achieving that aim.

The study showed an astonishing 82% slowing of Alzheimer's progression in treated patients vs. controls and an actual improvement in activities of daily living over a six-month period.

Ken Mariash, CEO

The remarkable effectiveness did not surprise the neuroscientists at the Cambridge, Mass.-based company. "We are starting to look at pretty much every neurological disease as a network dysfunction," Mariash said. "When you use a drug, you hope that the drug does the job by going through the bloodstream, through the blood-brain barrier and up into the appropriate region, but it will affect nearly every region of the brain, it will not be specific to a specific network operation. With brain stimulation, you can go directly to the source of the problem and affect the network that you want to modulate."

"We can induce specific activity at specific frequencies with our intervention and so bypass all those issues and you start to restore activity directly," added Emiliano Santarnecchi, co-founder of Sinaptica, associate professor of Radiology, Harvard Medical School; director, Precision Neuroscience & Neuromodulation program and director, Network Control Laboratory at the Gordon Center for Medical Imaging at Massachusetts General Hospital in Boston.

Emiliano Santarnecchi, co-founder

Studies going back to the 90s showed that transcranial magnetic stimulation (TMS) induced plasticity in the brain and demonstrated that plasticity is the key mechanism of memory, Santarnecchi noted.

Individualized, precise stimulation is key

Sinaptica uses repetitive TMS (rTMS) to target the part of the brain it believes to be most affected by Alzheimer's early in the disease, the precuneus region. To that technology, which is FDA approved for depression and obsessive-compulsive disorders, the company added neuronavigation.

"That means we can come within millimeter precision every time, reproducibly to exactly the same spot," Mariash said. "The real estate in the brain is very dense. If you're off by even a few millimeters, you cannot get the desired effect or even worse, you could induce off-target effects."

The neuronavigation, originally designed for brain surgery, also enables the team to see exactly what is happening in the brain by marking where the brain is stimulated on a 3D map of the brain made from the patient's brain MRI. The navigation enables "pulse-by-pulse adjustment of the stimulation, and we see a tremendous improvement in results and also the reliability of the intervention," Santarnecchi told *BioWorld*.

"Every patient's brain responds uniquely to TMS, and we know that because we look at the TMS EEG signals. We fire once to the precuneus and we listen to the reverberations around the network using 64-channel EEG, and we can see the propagation throughout the network of those signals. It forms a fingerprint

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pattern unique to every patient, so we calibrate the therapy based on the responses that we see in the network to make sure we get the right resonance and engagement of the default mode network."

More than 80% slowing across all measures

The phase II *Brain* study included 50 patients with mild to moderate Alzheimer's disease, assigned on a 1:1 ratio to precuneus stimulation with rTMS or a sham treatment over a 24-week period. Patients with precuneus stimulation maintained stable performance on the primary endpoint, the Clinical Dementia Rating Scale-Sum of Boxes score and had significantly better performances on the Alzheimer's Disease Assessment Scale-Cognitive Subscale, Mini-Mental State Examination and Alzheimer's Disease cooperative Study-Activities of Daily Living (ADL) scale. They also demonstrated an enhancement of local gamma oscillations. In contrast, the sham group showed deterioration across all measures.

Overall, the treated group showed a more than 80% slowing of dementia progression across all endpoints.

"The primary endpoint was deliberately chosen to be on par with those pharmacological therapies. We designed the phase II to really put us in the same category of efficacy as those major drug trials," Mariash noted. "And they didn't progress at all in six months, which is really remarkable, where the sham group did progress quite a lot. The separation was over eight points on the ADL scale."

Notably, the trial included patients with moderate dementia. "The drugs today are more focused on mild cognitive impairment and mild dementia patients. We think that's because every drug that's gone after mild to moderate patients has failed. It's commonly accepted that [moderate] patients are very difficult to arrest the disease progression once they're in that decline," Mariash said. "So that made the finding even more remarkable showing 82% disease slowing in a really hard to treat patient population."